FORM PTO-1390 (REV. 11-2000) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY 'S DOCKET NUMBER: A0000104-01-SMH

U S APPLICATION NO (If known, see 37 CFR 1 5): 10/031149

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US00/18346	5 July 2000	July 16, 1999

TITLE OF INVENTION
Method for Treating Chronic Pain Using Mek Inhibitors

APPLICANT(S) FOR DO/EO/US BARRETT, Stephen Douglas, BRIDGES, Alexander James, DIXON, Alistair, LEE, Kevin, PINNOCK, Robert Denham, TECLE, Haile, ZHANG, Lu-Yan

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☑ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☑ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☑ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☑ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☐ Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☑ Other items or information:
    International Search Report (PCT/ISA/210)
    International Preliminary Examination Report (PCT/IPEA/409)
    Certificate of Mailing by Express Mail

JC13 Rec'd PCT/PTO 15 JAN 2002

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
10/031149	PCT/US00/18346	A0000104-01-SMH

21. ☑ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**

CALCULATIONS PTO USE ONLY		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☑ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	33 - 20 =	13	x **$18.00**	$ 234.00	
Independent claims	1 - 3 =		x **$80.00**	$ 0.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$270.00**	$	
TOTAL OF ABOVE CALCULATIONS =				$ 1,224.00	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.			+	$	
SUBTOTAL =				$	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$ 1,224.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$ 1,224.00	
				Amount to be refunded:	$
				charged:	$

a. ☐ A check in the amount of $ _____ to cover the above fees is enclosed.

b. ☑ Please charge my Deposit Account No. 23-0455 in the amount of $ 1,224.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☑ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 23-0455 . A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

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42,640
REGISTRATION NUMBER

METHOD FOR TREATING CHRONIC PAIN USING MEK INHIBITORS

BACKGROUND

The invention features a method for treating chronic pain using MEK inhibitors. Chronic pain includes neuropathic pain, and chronic inflammatory pain.

Abnormality anywhere in a nerve pathway disrupts nerve signals, which in turn are abnormally interpreted in the brain, causing neuropathic pain. Neuropathic pain may be, for example, a deep ache, a burning sensation, or hypersensitivity to touch. Diseases or conditions associated with neuropathic pain include, without limitation, diabetic neuropathy, causalgia, plexus avulsion, neuroma, vasculitis, crush injury, viral infections (e.g., herpes virus infection or HIV), constriction injury, tissue injury, nerve injury from the periphery to the central nervous system, limb amputation, hypothyroidism, uremia, chronic alcoholism, post-operative pain, arthritis, back pain, and vitamin deficiencies.

Infections such as herpes zoster (shingles) can cause nerve inflammation and produce postherpetic neuralgia, a chronic burning localized to the area of viral infection. Hyperalgesia is when an already noxious stimulus becomes more painful, and allodynia, when a previously non-noxious stimulus becomes painful (such as contact of clothing or a breeze). Reflex sympathetic dystrophy is accompanied by swelling and sweating or changes in local blood flow, tissue atrophy, or osteoporosis. Causalgia, including severe burning pain and swelling, sweating, and changes in blood flow, may follow an injury or disease of a major nerve such as the sciatic nerve. Some types of chronic low back pain can have a neuropathic component (e.g., sciatica, postpoliomyelitis and CPRM). Neuropathic pain may also be induced by cancer or chemotherapy.

Neuropathic pain is currently treated with anticonvulsants such as carbamazepine and antidepressants such as amitryptaline. NSAIDS and opioids generally have little effect (*Fields et al 1994 Textbook of Pain p 991-996 (pub: Churchill Livingstone), James & Page 1994 J.Am.Pediatr.Med.Assoc, 8: 439-447, Galer, 1995 Neurology 45 S17-S25.*

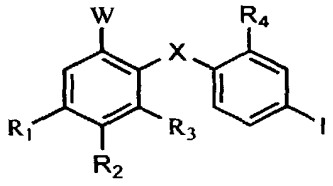
Neuropathic conditions that have been treated with gabapentin include: postherpetic neuralgia, postpoliomyelitis, CPRM, HIV-related neuropathy, trigeminal neuralgia, and reflex sympathetic dystrophy (RSD).

The generally weak efficacy of antiinflammatory agents suggests that the mechanism for chronic pain is separate from hyperalgesia.

SUMMARY OF THE INVENTION

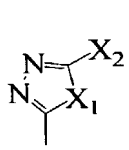
The invention features a method for treating chronic pain, which method includes the step of administering a composition including a MEK inhibitor to a patient in need of such treatment. Chronic pain includes neuropathic pain, idiopathic pain, and pain associated with vitamin deficiencies, uremia, hypothyroidism post-operative pain, arthritis, back pain, and chronic alcoholism. The invention also features compositions as disclosed, formulated for the treatment of chronic pain. Such a composition may include one or more MEK inhibitor compounds having a structure disclosed in patent application PCT/US99/30416, international filing date December 21, 1999.

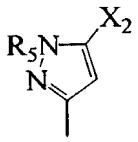
Examples of MEK inhibitors include a compound having the formula (I) below:



I

W is one of the following formulae (i) – (xiii):


(i)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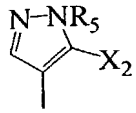
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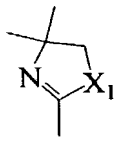
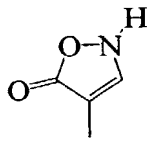

(iV)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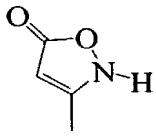
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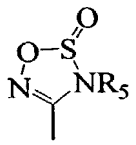
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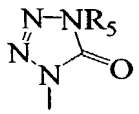
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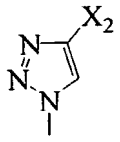
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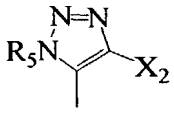
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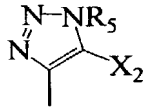
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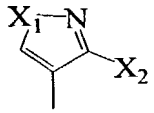
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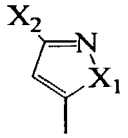
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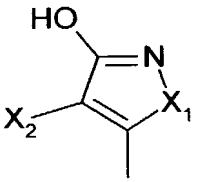
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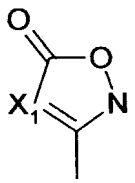
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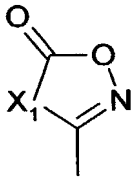
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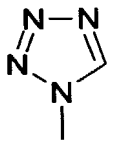

(xvii)

X_1 is O, S, or NR_F. X_2 is OH, SH, or NHR_E. Each of R_E and R_F is H or C_{1-4} alkyl; each of R_1 and R_2 is independently selected from H, F, NO_2, Br and Cl; R_1 can also be $SO_2NR_GR_H$, or R_1 and R_2 together with the benzene ring to which they are attached constitute an indole, isoindole, benzofuran, benzothiophene, indazole, benzimidazole, or benzthioazole. R_3 is selected from H and F; each of R_G, R_H, and R_4 is independently selected from H, Cl and CH_3. R_5 is H or C_{1-4} alkyl. Each hydrocarbon radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, hydroxyl, amino, (amino)sulfonyl, and NO_2. Each heterocyclic radical

above is optionally substituted with between 1 and 3 substituents independently selected from halo, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-4} alkenyl, C_{3-4} alkynyl, phenyl, hydroxyl, amino, (amino)sulfonyl, and NO_2, wherein each substituent alkyl, cycloalkyl, alkenyl, alkynyl or phenyl is in turn optionally substituted with between 1 and 2 substituents independently selected from halo, C_{1-2} alkyl, hydroxyl, amino, and NO_2. The invention also features a pharmaceutically acceptable salt or C_{1-8} ester of a disclosed compound. For example, the disclosed alcohol compounds may form esters having the structure obtained by replacing the H of a hydroxyl group with a $-C(=O)C_{1-7}$ acyl group.

Preferred embodiments of the invention include methods of using one or more of the following compounds:

(a) said MEK inhibitor has a structure selected from: 2,4-bis-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-benzoic acid; 5-[3,4difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; (2,3-difluoro-6-[1,3,4]oxadiazol-2-yl-phenyl)(-(4-iodo-2-methyl-phenyl)-amine; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[3,4difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4*H*-[1,2,4]triazole-3-ylamine; and 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4*H*-[1,2,4]triazole-3-thiol; and

(b) said MEK inhibitor has the structure selected from: 2,4-bis-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-benzoic acid.

Other aspects of the invention are provided in the description, examples and claims below.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a bar graph representing the paw withdrawal threshold (PWT) in grams as a function of time in days. The empty, cross-hatched, and single-

hatched bars are vehicle, PD 198306, and pregabalin, respectively. The arrows indicate time of drug administration (30 mg/kg, p.o.).

FIG 2. is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days. Baseline (BL) measurements were taken before treatment. Animals received a single p.o. administration of PD 198306 (3-30mg/kg), or pregabalin (30mg/kg) and withdrawal thresholds were re-assessed 1h after treatment. Treatments were repeated twice a day for two days. Results are expressed median ± 1st and 3rd quartiles. *P<0.05, **P<0.01, ***P<0.001 significantly different from vehicle treated animals (Mann-Whitney t test; n=7-8).

FIG. 3. is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days. Baseline (BL) measurements were taken before treatment. Animals received a single p.o. administration of PD 198306 (3-30mg/kg), or pregabalin (30mg/kg) and withdrawal thresholds were re-assessed 1h after treatment. Treatments were repeated twice a day for two days. Results are expressed median ± 1st and 3rd quartiles. **P<0.01 significantly different from vehicle treated animals (Mann-Whitney t test; n=6).

FIG. 4. is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days. Baseline (BL) measurements were taken before treatment. Animals received a single i.t. administration of PD 198306 (1-30μg/10μl), or pregabalin (100μg/10μl) and withdrawal thresholds were re-assessed at 30min, 1h and 2h after treatment. Results are expressed median ± 1st and 3rd quartiles. *P<0.05, ***P<0.001 significantly different from vehicle treated animals (Mann-Whitney t test; n=7-9).

FIG. 5. is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days.

Baseline (BL) measurements were taken before treatment. Animals received a single i.t. administration of PD 198306 (1-30μg/10μl), or pregabalin (100μg/10μl) and withdrawal thresholds were re-assessed at 30min, 1h and 2h after treatment. Results are expressed median ± 1st and 3rd quartiles. *P<0.05, **P<0.01, ***P<0.001 significantly different from vehicle treated animals (Mann-Whitney t test; n=6-8).

FIG. 6 is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days . Animals received a single intraplantar (i.pl.) administration of PD 198306 (3mg/100μl), or an intrathecal injection of PD 198306 (30μg/10μl) and withdrawal thresholds were re-assessed 1h after treatment. Results are expressed median ± 1st and 3rd quartiles. **P<0.01 significantly different from vehicle treated animals (Mann-Whitney t test; n=6-9).

FIG. 7. is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments as a function of time in days. Animals received a single intraplantar (i.pl.) administration of PD 198306 (3mg/100μl), or an intrathecal injection of PD 198306 (30μg/10μl) and withdrawal thresholds were re-assessed 1h after treatment. Results are expressed median ± 1st and 3rd quartiles. **P<0.01 significantly different from vehicle treated animals (Mann-Whitney t test; n=6).

FIG. 8 is a bar graph representing the force required in grams to elicit paw withdrawal using von Frey hair filaments. Baseline (BL) measurements were taken before treatment. Animals received a single i.t. administration of PD219622, PD297447, PD 184352, or PD 254552 (30μg/10μl), or pregabalin (100μg/10μl) and withdrawal thresholds were re-assessed at 30min, 1h and 2h after treatment. Results are expressed median ± 1st and 3rd quartiles. *P<0.05, **P<0.01, ***P<0.001 significantly different from vehicle treated animals (Mann-Whitney t test; n=7-8).

DETAILED DESCRIPTION

The compounds disclosed herein are pharmaceutically active, for example, they inhibit MEK. MEK enzymes are dual specificity kinases involved in, for example, immunomodulation, inflammation, and proliferative diseases such as cancer and restenosis.

Proliferative diseases are caused by a defect in the intracellular signaling system, or the signal transduction mechanism of certain proteins. Defects include a change either in the intrinsic activity or in the cellular concentration of one or more signaling proteins in the signaling cascade . The cell may produce a growth factor that binds to its own receptors, resulting in an autocrine loop, which continually stimulates proliferation. Mutations or overexpression of intracellular signaling proteins can lead to spurious mitogenic signals within the cell. Some of the most common mutations occur in genes encoding the protein known as Ras, a G-protein that is activated when bound to GTP, and inactivated when bound to GDP. The above-mentioned growth factor receptors, and many other mitogenic receptors, when activated, lead to Ras being converted from the GDP-bound state to the GTP-bound state. This signal is an absolute prerequisite for proliferation in most cell types. Defects in this signaling system, especially in the deactivation of the Ras-GTP complex, are common in cancers, and lead to the signaling cascade below Ras being chronically activated.

Activated Ras leads in turn to the activation of a cascade of serine/threonine kinases. One of the groups of kinases known to require an active Ras-GTP for its own activation is the Raf family. These in turn activate MEK (e.g., MEK_1 and MEK_2) which then activates MAP kinase, ERK (ERK_1 and ERK_2). Activation of MAP kinase by mitogens appears to be essential for proliferation; constitutive activation of this kinase is sufficient to induce cellular transformation. Blockade of downstream Ras signaling, for example by use of a dominant negative Raf-1 protein, can completely inhibit mitogenesis, whether induced from cell surface receptors or from oncogenic Ras mutants. Although Ras is not itself a protein kinase, it participates in the activation of

Raf and other kinases, most likely through a phosphorylation mechanism. Once activated, Raf and other kinases phosphorylate MEK on two closely adjacent serine residues, S^{218} and S^{222} in the case of MEK-1, which are the prerequisite for activation of MEK as a kinase. MEK in turn phosphorylates MAP kinase on both a tyrosine, Y^{185}, and a threonine residue, T^{183}, separated by a single amino acid.

This double phosphorylation activates MAP kinase at least 100-fold. Activated MAP kinase can then catalyze the phosphorylation of a large number of proteins, including several transcription factors and other kinases. Many of these MAP kinase phosphorylations are mitogenically activating for the target protein, such as a kinase, a transcription factor, or another cellular protein. In addition to Raf-1 and MEKK, other kinases activate MEK, and MEK itself appears to be a signal integrating kinase. Current understanding is that MEK is highly specific for the phosphorylation of MAP kinase. In fact, no substrate for MEK other than the MAP kinase , ERK, has been demonstrated to date and MEK does not phosphorylate peptides based on the MAP kinase phosphorylation sequence, or even phosphorylate denatured MAP kinase. MEK also appears to associate strongly with MAP kinase prior to phosphorylating it, suggesting that phosphorylation of MAP kinase by MEK may require a prior strong interaction between the two proteins. Both this requirement and the unusual specificity of MEK are suggestive that it may have enough difference in its mechanism of action to other protein kinases that selective inhibitors of MEK, possibly operating through allosteric mechanisms rather than through the usual blockade of the ATP binding site, may be found.

The effect of the MEK inhibitor PD 198306 has been investigated in two animal models of neuropathic pain by assessing static allodynia with von Frey hairs.

Oral administration of PD 198306 (3-30mg/kg) had no effect in the model of chronic constriction injury of the sciatic nerve (CCI). However, after repeated administration (3 doses over two days) it had a transient effect in the diabetic neuropathy model (streptozocin). This may be due to disorders of the blood-

brain barrier induced by the diabetic condition in these animals, thus allowing central action of the compound. Intrathecal administration of PD 198306 (1-30μg) dose-dependently blocked static allodynia in both the streptozocin and the CCI models of neuropathic pain, with minimum effective doses (MED) of 3 and 10μg respectively. The highest dose used (30μg) totally blocked the maintenance of static allodynia, for up to 1h. Intraplantar administration of PD 198306 (3mg/100μl) at a dose 100-fold higher than the dose shown to be effective intrathecally (30μg/10μl) had no effect on static allodynia in either of the neuropathic pain models. This finding confirms the lack of effect seen after systemic administration and suggests a central site of action for the compound.

From this study we can suggest the use of MEK inhibitors as potential new therapeutic tools for chronic pain. The study of potential side-effects, especially related to memory, of future brain-penetrant MEK inhibitors will indicate the therapeutic window for this novel class of compounds in the treatment of pain.

A. Terms

Certain terms are defined below and by their usage throughout this disclosure.

Alkyl groups include aliphatic (i.e., hydrocarbyl or hydrocarbon radical structures containing hydrogen and carbon atoms) with a free valence. Alkyl groups are understood to include straight chain and branched structures. Examples include methyl, ethyl, propyl, isopropyl, butyl, n-butyl, isobutyl, t-butyl, pentyl, isopentyl, 2,3-dimethylpropyl, hexyl, 2,3-dimethylhexyl, 1,1-dimethylpentyl, heptyl, and octyl. Cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

Alkyl groups can be substituted with 1, 2, 3 or more substituents which are independently selected from halo (fluoro, chloro, bromo, or iodo), hydroxy, amino, alkoxy, alkylamino, dialkylamino, cycloalkyl, aryl, aryloxy, arylalkyloxy, heterocyclic radical, and (heterocyclic radical)oxy. Specific examples include fluoromethyl, hydroxyethyl, 2,3-dihydroxyethyl, (2- or 3-furanyl)methyl, cyclopropylmethyl, benzyloxyethyl, (3-pyridinyl)methyl, (2- or 3-furanyl)methyl, (2-thienyl)ethyl, hydroxypropyl, aminocyclohexyl, 2-dimethylaminobutyl, methoxymethyl, *N*-pyridinylethyl, diethylaminoethyl, and cyclobutylmethyl.

Alkenyl groups are analogous to alkyl groups, but have at least one double bond (two adjacent sp^2 carbon atoms). Depending on the placement of a double bond and substituents, if any, the geometry of the double bond may be *entgegen* (E), or *zusammen* (Z), *cis*, or *trans*. Similarly, alkynyl groups have at least one triple bond (two adjacent sp carbon atoms). Unsaturated alkenyl or alkynyl groups may have one or more double or triple bonds, respectively, or a mixture thereof; like alkyl groups, unsaturated groups may be straight chain or branched, and they may be substituted as described both above for alkyl groups and throughout the disclosure by example. Examples of alkenyls, alkynyls, and substituted forms include cis-2-butenyl, trans-2-butenyl, 3-butynyl, 3-phenyl-2-propynyl, 3-(2'-fluorophenyl)-2-propynyl, 3-methyl(5-phenyl)-4-pentynyl, 2-hydroxy-2-propynyl, 2-methyl-2-propynyl, 2-propenyl, 4-hydroxy-3-butynyl, 3-(3-fluorophenyl)-2-propynyl, and 2-methyl-2-

propenyl. In formula (I), alkenyls and alkynyls can be C_{2-4} or C_{2-8}, for example, and are preferably C_{3-4} or C_{3-8}.

More general forms of substituted hydrocarbon radicals include hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, hydroxycycloalkyl, hydroxyaryl, and corresponding forms for the prefixes amino-, halo- (e.g., fluoro-, chloro-, or bromo-), nitro-, alkyl-, phenyl-, cycloalkyl- and so on, or combinations of substituents. According to formula (I), therefore, substituted alkyls include hydroxyalkyl, aminoalkyl, nitroalkyl, haloalkyl, alkylalkyl (branched alkyls, such as methylpentyl), (cycloalkyl)alkyl, phenylalkyl, alkoxy, alkylaminoalkyl, dialkylaminoalkyl, arylalkyl, aryloxyalkyl, arylalkyloxyalkyl, (heterocyclic radical)alkyl, and (heterocyclic radical)oxyalkyl. R_1 thus includes hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, hydroxycycloalkyl, hydroxyaryl, aminoalkyl, aminoalkenyl, aminoalkynyl, aminocycloalkyl, aminoaryl, alkylalkenyl, (alkylaryl)alkyl, (haloaryl)alkyl, (hydroxyaryl)alkynyl, and so forth. Similarly, R_A includes hydroxyalkyl and aminoaryl, and R_B includes hydroxyalkyl, aminoalkyl, and hydroxyalkyl(heterocyclic radical)alkyl.

Heterocyclic radicals, which include but are not limited to heteroaryls, include: furyl, oxazolyl, isoxazolyl, thiophenyl, thiazolyl, pyrrolyl, imidazolyl, 1,3,4-triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyridazinyl, indolyl, and their nonaromatic counterparts. Further examples of heterocyclic radicals include piperidyl, quinolyl, isothiazolyl, piperidinyl, morpholinyl, piperazinyl, tetrahydrofuryl, tetrahydropyrrolyl, pyrrolidinyl, octahydroindolyl, octahydrobenzothiofuranyl, and octahydrobenzofuranyl.

Selective MEK 1 or MEK 2 inhibitors are those compounds which inhibit the MEK 1 or MEK 2 enzymes, respectively, without substantially inhibiting other enzymes such as MKK3, PKC, Cdk2A, phosphorylase kinase, EGF, and PDGF receptor kinases, and C-src. In general, a selective MEK 1 or MEK 2 inhibitor has an IC_{50} for MEK 1 or MEK 2 that is at least one-fiftieth (1/50) that of its IC_{50} for one of the above-named other enzymes. Preferably, a selective inhibitor has an IC_{50} that is at least 1/100, more preferably 1/500, and even more preferably 1/1000, 1/5000, or less than that of its IC_{50} or one or more of the above-named enzymes.

B. Compounds

One aspect of the invention features the disclosed compounds shown in formula (I) in the Summary section.

Embodiments of the invention include compounds wherein: (a) R_1 is bromo or chloro; (b) R_2 is fluoro; (c) R_3 is H; (d) each of R_2 and R_3 is H; (e) each of R_2 and R_3 is fluoro; (f) R_1 is bromo; (g) each of R_1, R_2 and R_3 is fluoro; (h) R_2 is nitro; (i) R_3 is H; (j) R_4 is chloro; (k) R_4 is methyl; (l) R_5 is H; (m) R_5 is CH_3; (n) X_1 is O or S; (o) X_1 is NH or NCH_3; (p) X_2 is OH, SH, or NH_2; (q) X_2 is OH; (r) X_2 is NHR_E; (s) R_4 is H; (t) R_4 is chloro or methyl; or combinations thereof.

Preferably, where one of the substituents on a heterocyclic radical is an alkenyl or alkynyl group, the double or triple bond, respectively, is not adjacent the point of attachment when it is a heteroatom. For example, in such a situation, the substituent is preferably prop-2-ynyl, or but-2 or 3-enyl, and less preferably prop-1-ynyl or but-1-enyl.

Examples of compounds include: [5-fluoro-2-(1H-tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [2,3-difluoro-6-(1H-tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)- amine; (4-iodo-2-methyl-phenyl)-[2,3,4-trifluoro-6-(1H-tetrazol-5-yl)-phenyl]-amine; [4-bromo-2,3-difluoro-6-(1H-tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [5-fluoro-4-nitro-2-(1H-tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [2-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-5-fluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [6-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-2,3-difluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [6-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-2,3,4-trifluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [4-bromo-6-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-2,3-difluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [2-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-5-fluoro-4-nitro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-

phenylamino)-5-nitro-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; and 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-[1,2,4]triazol-3-ol.

Further examples include: 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-

thiol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; and 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-[1,2,4]triazole-3-thiol.

Additional examples are: 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isothiazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isoxazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-1H-pyrazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-

phenylamino)-phenyl]-isothiazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isothiazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isoxazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol; 1-methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol; and 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-1-methyl-1H-pyrazol-3-ol.

The invention also features compounds such as: 5-[2-(2-amino-4-iodo-phenylamino)-4-fluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-3,4-difluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-3,4,5-trifluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-5-bromo-3,4-difluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-4-fluoro-5-nitro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 3-methyl-5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3H-[1,2,3]triazol-4-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2-methyl-2H-pyrazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2-methyl-2H-pyrazol-3-ol; 2-methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-pyrazol-3-ol; 4-[5-

bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2-methyl-2H-pyrazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-2-methyl-2H-pyrazol-3-ol; 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1,4-dihydro-tetrazol-5-one; 1-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-[1,2,3]triazol-4-ol; 1-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-[1,2,3]triazol-4-ol; 1-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-[1,2,3]triazol-4-ol; 1-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-[1,2,3]triazol-4-ol; and 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-1H-[1,2,3]triazol-4-ol.

Further examples of the invention include 3-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-2H-isoxazol-5-one; [5-fluoro-2-(2-oxo-2,3-dihydro-2I>4_-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [2,3-difluoro-6-(2-oxo-2,3-dihydro-2I>4_-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; (4-Iodo-2-methyl-phenyl)-[2,3,4-trifluoro-6-(2-oxo-2,3-dihydro-2I>4_-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-amine; [4-bromo-2,3-difluoro-6-(2-oxo-2,3-dihydro-2I>4_-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [5-fluoro-4-nitro-2-(2-oxo-2,3-dihydro-2I>4_-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; 4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-

one; and 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-isoxazol-5-one.

Further compounds, where R_1 can also be $SO_2NR_GR_H$, or R_1 and R_2 together with the benzene ring to which they are attached constitute an indole, isoindole, benzofuran, benzothiophene, indazole, benzimidazole, or benzthioazole, include the following groups:

Group 1

(1) 2-Fluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-N-methyl-benzenesulfonamide

(3) 2,3-Difluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-4-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzenesulfonamide

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-N-methyl-N-(3-morpholin-4-yl-propyl)-benzenesulfonamide

(5) 2-Fluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-4-(4-iodo-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethyl]-benzenesulfonamide

(6) N-(2-Dimethylamino-ethyl)-2-fluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-4-(4-iodo-phenylamino)-N-methyl-benzenesulfonamide

Group 2

(1) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro- benzenesulfonamide

(3) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonamide

(5) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

(6) 4-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-5-(4-iodo-phenylamino)-benzenesulfonamide

Group 2b

(1) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-4-(4-iodo-phenylamino)-N-methyl-N-(3-morpholin-4-yl-propyl)-benzenesulfonamide

(3) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

(5) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-N-[3-(4-methyl-piperazin-1-yl)-propyl]-benzenesulfonamide

(6) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-N-(3-piperidin-1-yl-propyl)-benzenesulfonamide

Group 3

(1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-mercapto-1,3,4-oxadiazol-2-yl)-benzenesulfonamide

(2) 2-Fluoro-5-(4-iodo-phenylamino)-4-(5-mercapto-1,3,4-oxadiazol-2-yl)-benzenesulfonamide

(3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-mercapto-1,3,4-oxadiazol-2-yl)-benzenesulfonamide

(4) 2-Fluoro-4-(4-iodo-phenylamino)-5-(5-mercapto-1,3,4-oxadiazol-2-yl)-benzenesulfonamide

(5) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-mercapto-1,3,4-oxadiazol-2-yl)-benzenesulfonamide

(6) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-mercapto-1,3,4-oxadiazol-2-yl)-benzenesulfonamide

Group 4

(1) 2-Fluoro-5-(5-hydroxy-1,3,4-thiadiazol-2-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 2-Fluoro-4-(5-hydroxy-1,3,4-thiadiazol-2-yl)-5-(4-iodo-phenylamino)-benzenesulfonamide

(3) 2,3-Difluoro-5-(5-hydroxy-1,3,4-thiadiazol-2-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 2-Fluoro-5-(5-hydroxy-1,3,4-thiadiazol-2-yl)-4-(4-iodo-phenylamino)-benzenesulfonamide

(5) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-hydroxy-1,3,4-thiadiazol-2-yl)-benzenesulfonamide

(6) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-hydroxy-1,3,4-thiadiazol-2-yl)-benzenesulfonamide

Group 5

(1) 5-(5-Amino-1,3,4-thiadiazol-2-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 4-(5-Amino-1,3,4-thiadiazol-2-yl)-5-(4-iodo-phenylamino)-2-mercapto-benzenesulfonamide

(3) 5-(5-Amino-1,3,4-thiadiazol-2-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 5-(5-Amino-1,3,4-thiadiazol-2-yl)-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

(5) 5-(5-Amino-1,3,4-thiadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonamide

(6) 5-(5-Amino-1,3,4-thiadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-benzenesulfonamide

Group 6

(1) 2-Fluoro-5-(5-hydroxy-4H-1,2,4-triazol-3-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 2-Fluoro-4-(5-hydroxy-4H-1,2,4-triazol-3-yl)-5-(4-iodo-phenylamino)-benzenesulfonamide

(3) 2,3-Difluoro-5-(5-hydroxy-4H-1,2,4-triazol-3-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 5-[4-(2-Dimethylamino-ethyl)-5-hydroxy-4H-1,2,4-triazol-3-yl]-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

(5) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-hydroxy-4H-1,2,4-triazol-3-yl)-benzenesulfonamide

(6) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-hydroxy-4-methyl-4H-1,2,4-triazol-3-yl)-benzenesulfonamide

Group 7

(1) 5-(5-Amino-4H-1,2,4-triazol-3-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 4-(5-Amino-4H-1,2,4-triazol-3-yl)-2-fluoro-5-(4-iodo-phenylamino)-benzenesulfonamide

(3) 5-(5-Amino-4-methyl-4H-1,2,4-triazol-3-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 5-[5-Amino-4-(3-dimethylamino-propyl)-4H-1,2,4-triazol-3-yl]-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

(5) 5-(5-Amino-4H-1,2,4-triazol-3-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonamide

(6) 5-(5-Amino-4-methyl-4H-1,2,4-triazol-3-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-benzenesulfonamide

Group 8

(1) 2-Fluoro-5-(3-hydroxy-isoxazol-5-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 2-Fluoro-4-(3-hydroxy-isoxazol-5-yl)-5-(4-iodo-phenylamino)-benzenesulfonamide

(3) 2,3-Difluoro-5-(3-hydroxy-isoxazol-5-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 2-Fluoro-5-(3-hydroxy-isoxazol-5-yl)-4-(4-iodo-phenylamino)-benzenesulfonamide

(5) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(3-hydroxy-isoxazol-5-yl)-benzenesulfonamide

(6) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(3-hydroxy-isoxazol-5-yl)-benzenesulfonamide

Group 9

(1) 5-(3-Amino-isoxazol-5-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 4-(3-Amino-isoxazol-5-yl)-2-bromo-5-(4-iodo-phenylamino)-benzenesulfonamide

(3) 5-(3-Amino-isoxazol-5-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 5-(3-Amino-isoxazol-5-yl)-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

(5) 5-(3-Amino-isoxazol-5-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonamide

(6) 5-(3-Amino-isoxazol-5-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-benzenesulfonamide

Group 10

(1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(3-mercapto-isoxazol-5-yl)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(3-mercapto-isoxazol-5-yl)-benzenesulfonamide

(3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(3-mercapto-isoxazol-5-yl)-benzenesulfonamide

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(3-mercapto-isoxazol-5-yl)-benzenesulfonamide

(5) 2-Fluoro-4-(4-iodo-phenylamino)-5-(3-mercapto-isoxazol-5-yl)-benzenesulfonamide

(6) 2-Bromo-5-(4-iodo-phenylamino)-4-(3-mercapto-isoxazol-5-yl)-benzenesulfonamide

Group 11

(1) 2-Fluoro-5-(3-hydroxy-isoxazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(3-hydroxy-isoxazol-4-yl)-benzenesulfonamide

(3) 2,3-Difluoro-5-(3-hydroxy-isoxazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(3-hydroxy-isoxazol-4-yl)-benzenesulfonamide

(5) 2-Fluoro-5-(3-hydroxy-isoxazol-4-yl)-4-(4-iodo-phenylamino)-benzenesulfonamide

(6) 2-Bromo-4-(3-hydroxy-isoxazol-4-yl)-5-(4-iodo-phenylamino)-benzenesulfonamide

Group 12

(1) 5-(3-Amino-isoxazol-4-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 5-(3-Amino-isoxazol-4-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-benzenesulfonamide

(3) 5-(3-Amino-isoxazol-4-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 5-(3-Amino-isoxazol-4-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonamide

(5) 5-(3-Amino-isoxazol-4-yl)-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

(6) 4-(3-Amino-isoxazol-4-yl)-2-chloro-5-(4-iodo-phenylamino)-benzenesulfonamide

Group 13

(1) 5-(3-Amino-isoxazol-4-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 5-(3-Amino-isoxazol-4-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-benzenesulfonamide

(3) 5-(3-Amino-isoxazol-4-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 5-(3-Amino-isoxazol-4-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonamide"

(5) 5-(3-Amino-isoxazol-4-yl)-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

(6) 4-(3-Amino-isoxazol-4-yl)-2-chloro-5-(4-iodo-phenylamino)-benzenesulfonamide

Group 14

(1) 5-(2-Amino-5H-pyrrol-3-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 5-(2-Amino-5H-pyrrol-3-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-benzenesulfonamide

(3) 5-(2-Amino-5H-pyrrol-3-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 5-(2-Amino-5H-pyrrol-3-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonamide

(5) 5-(2-Amino-5H-pyrrol-3-yl)-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

(6) 4-(2-Amino-5H-pyrrol-3-yl)-2-chloro-5-(4-iodo-phenylamino)-benzenesulfonamide

Group 15

(1) 2-Fluoro-5-(5-hydroxy-1-methyl-1H-pyrazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-hydroxy-1H-pyrazol-4-yl)-benzenesulfonamide

(3) 2,3-Difluoro-5-(5-hydroxy-1H-pyrazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-hydroxy-1H-pyrazol-4-yl)-benzenesulfonamide

(5) 2-Fluoro-5-{5-hydroxy-1-[3-(4-methyl-piperazin-1-yl)-propyl]-1H-pyrazol-4-yl}-4-(4-iodo-phenylamino)-benzenesulfonamide

(6) 2-Fluoro-4-(5-hydroxy-1H-pyrazol-4-yl)-5-(4-iodo-phenylamino)-benzenesulfonamide

Group 16

(1) 2-Fluoro-5-(5-hydroxy-3-methyl-3H-1,2,3-triazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-benzenesulfonamide

(3) 2,3-Difluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-benzenesulfonamide

(5) 2-Fluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-4-(4-iodo-phenylamino)-benzenesulfonamide

(6) 2-Fluoro-5-{5-hydroxy-3-[2-(2-methoxy-ethoxy)-ethyl]-3H-1,2,3-triazol-4-yl}-4-(4-iodo-phenylamino)-benzenesulfonamide

Group 17

(1) 2-Fluoro-5-(5-hydroxy-3-methyl-3H-1,2,3-triazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)- benzenesulfonamide

(3) 2,3-Difluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-benzenesulfonamide

(5) 2-Fluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-4-(4-iodo-phenylamino)-benzenesulfonamide

(6) 2-Fluoro-5-{5-hydroxy-3-[2-(2-methoxy-ethoxy)-ethyl]-3H-1,2,3-triazol-4-yl}-4-(4-iodo-phenylamino)-benzenesulfonamide

Group 18

(1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

(3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

(5) 2-Fluoro-4-(4-iodo-phenylamino)-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

(6) 2,6-Difluoro-3-(4-iodo-phenylamino)-4-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

Group 19

(1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(4-methyl-5-oxo-4,5-dihydro-tetrazol-1-yl)- benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(4-methyl-5-oxo-4,5-dihydro-tetrazol-1-yl)- benzenesulfonamide

(3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

(5) 5-[4-(2-Dimethylamino-ethyl)-5-oxo-4,5-dihydro-tetrazol-1-yl]-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

(6) 2-Fluoro-5-(4-iodo-phenylamino)-4-(4-methyl-5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

Group 20

(1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(5) 2-Fluoro-4-(4-iodo-phenylamino)-5-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(6) 2-Fluoro-5-(4-iodo-phenylamino)-4-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

Group 21

(1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(2) 2,6-Difluoro-3-(4-iodo-phenylamino)-4-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(4) 2-Fluoro-4-(4-iodo-phenylamino)-5-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(5) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(6) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-N-methyl-5-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

Group 22

(1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide

(2) 2,6-Difluoro-3-(4-iodo-phenylamino)-4-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide

(3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide

(4) 2-Fluoro-4-(4-iodo-phenylamino)-5-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide

(5) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide

(6) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide

Group 23

(1) 5-[6-(4-Iodo-2-methyl-phenylamino)-1H-benzimidazol-5-yl]-1,3,4-oxadiazol-2-ol

(2) 5-[6-(4-Iodo-phenylamino)-benzofuran-5-yl]-1,3,4-oxadiazol-2-ol

(3) 5-[7-Fluoro-6-(4-iodo-2-methyl-phenylamino)-benzoxazol-5-yl]-1,3,4-oxadiazol-2-ol

(4) 5-[5-(4-Iodo-phenylamino)-benzofuran-6-yl]-1,3,4-oxadiazol-2-ol

(5) 5-[6-(2-Chloro-4-iodo-phenylamino)-7-fluoro-1,3-dihydro-isobenzofuran-5-yl]-1,3,4-oxadiazol-2-ol

(6) 5-[6-(2-Chloro-4-iodo-phenylamino)-1-methyl-1H-benzimidazol-5-yl]-1,3,4-oxadiazol-2-ol

Group 24

(1) 5-[2-Amino-6-(4-iodo-2-methyl-phenylamino)-1H-benzimidazol-5-yl]-1,3,4-oxadiazol-2-ol

(2) 5-[6-(4-Iodo-phenylamino)-benzo[b]thiophen-5-yl]-1,3,4-oxadiazol-2-ol

(3) 5-[7-Fluoro-6-(4-iodo-2-methyl-phenylamino)-benzothiazol-5-yl]-1,3,4-oxadiazol-2-ol

(4) 5-[5-(4-Iodo-phenylamino)-benzo[b]thiophen-6-yl]-1,3,4-oxadiazol-2-ol

(5) 5-[6-(2-Chloro-4-iodo-phenylamino)-7-fluoro-1,3-dihydro-benzo[c]thiophen-5-yl]-1,3,4-oxadiazol-2-ol

(6) 5-[6-(2-Chloro-4-iodo-phenylamino)-2-oxo-2,3-dihydro-1H-2$l>4_-2,1,3-benzothiadiazol-5-yl]-1,3,4-oxadiazol-2-ol

Group 25

(1) 5-[2-Amino-6-(4-iodo-2-methyl-phenylamino)-benzothiazol-5-yl]-1,3,4-oxadiazol-2-ol

(2) 5-[6-(4-Iodo-phenylamino)-1H-indol-5-yl]-1,3,4-oxadiazol-2-ol

(3) 5-[7-Fluoro-6-(4-iodo-2-methyl-phenylamino)-benzothiazol-5-yl]-1,3,4-oxadiazol-2-ol

(4) 5-[5-(4-Iodo-phenylamino)-1H-indol-6-yl]-1,3,4-oxadiazol-2-ol

(5) 5-[6-(2-Chloro-4-iodo-phenylamino)-7-fluoro-2,3-dihydro-1H-isoindol-5-yl]-1,3,4-oxadiazol-2-ol

(6) 5-[5-(2-Chloro-4-iodo-phenylamino)-1H-indazol-6-yl]-1,3,4-oxadiazol-2-ol

Group 26

(1) 5-[2-Amino-6-(4-iodo-2-methyl-phenylamino)-benzothiazol-5-yl]-1,3,4-oxadiazol-2-ol

(2) 5-[6-(4-Iodo-phenylamino)-1H-indol-5-yl]-1,3,4-oxadiazol-2-ol

(3) 5-[7-Fluoro-6-(4-iodo-2-methyl-phenylamino)-benzoxazol-5-yl]-1,3,4-oxadiazol-2-ol

(4) 5-[5-(4-Iodo-phenylamino)-benzoxazol-6-yl]-1,3,4-oxadiazol-2-ol

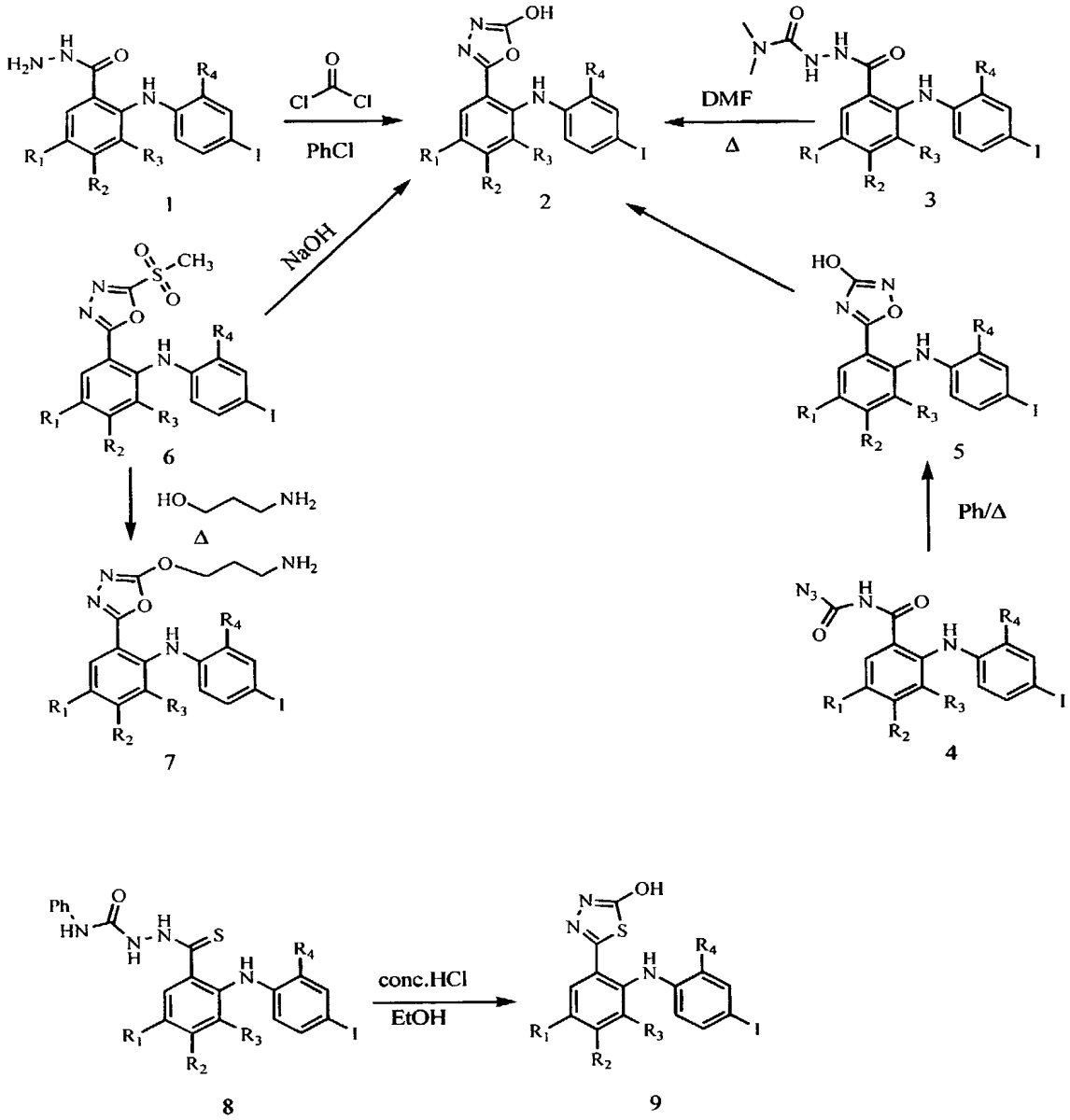
(5) 5-[6-(2-Chloro-4-iodo-phenylamino)-7-fluoro-2,3-dihydro-1H-isoindol-5-yl]-1,3,4-oxadiazol-2-ol

(6) 5-[5-(2-Chloro-4-iodo-phenylamino)-1H-indazol-6-yl]-1,3,4-oxadiazol-2-ol

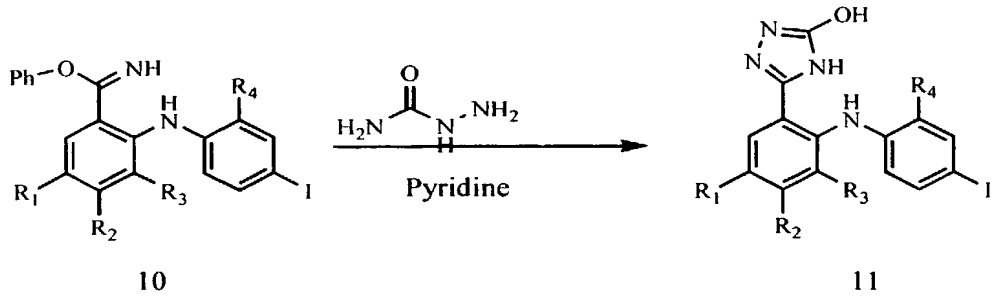
C. Synthesis

The disclosed compounds can be synthesized according to Schemes 1-25 or analogous variants thereof. These synthetic strategies are further exemplified in Examples 1-8 below. The solvent between compounds 4 and 5 in Scheme 1 is toluene (PhMe).

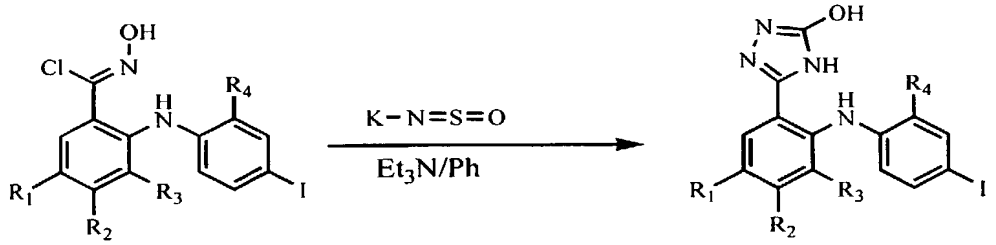
Scheme 1



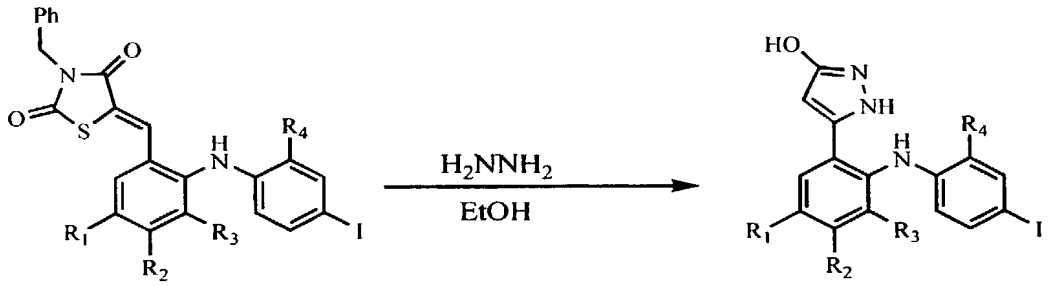
Scheme 2



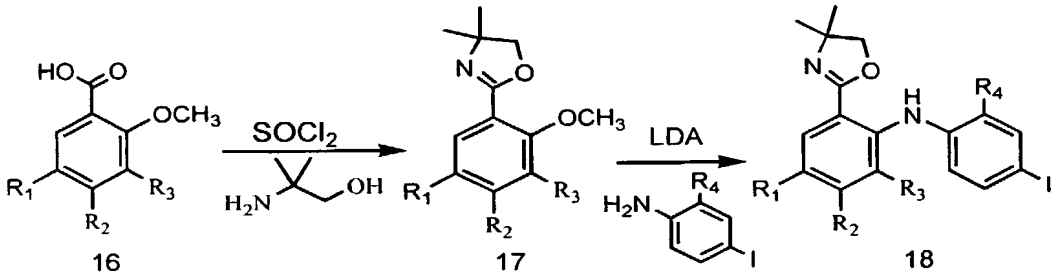
10 11



12 13

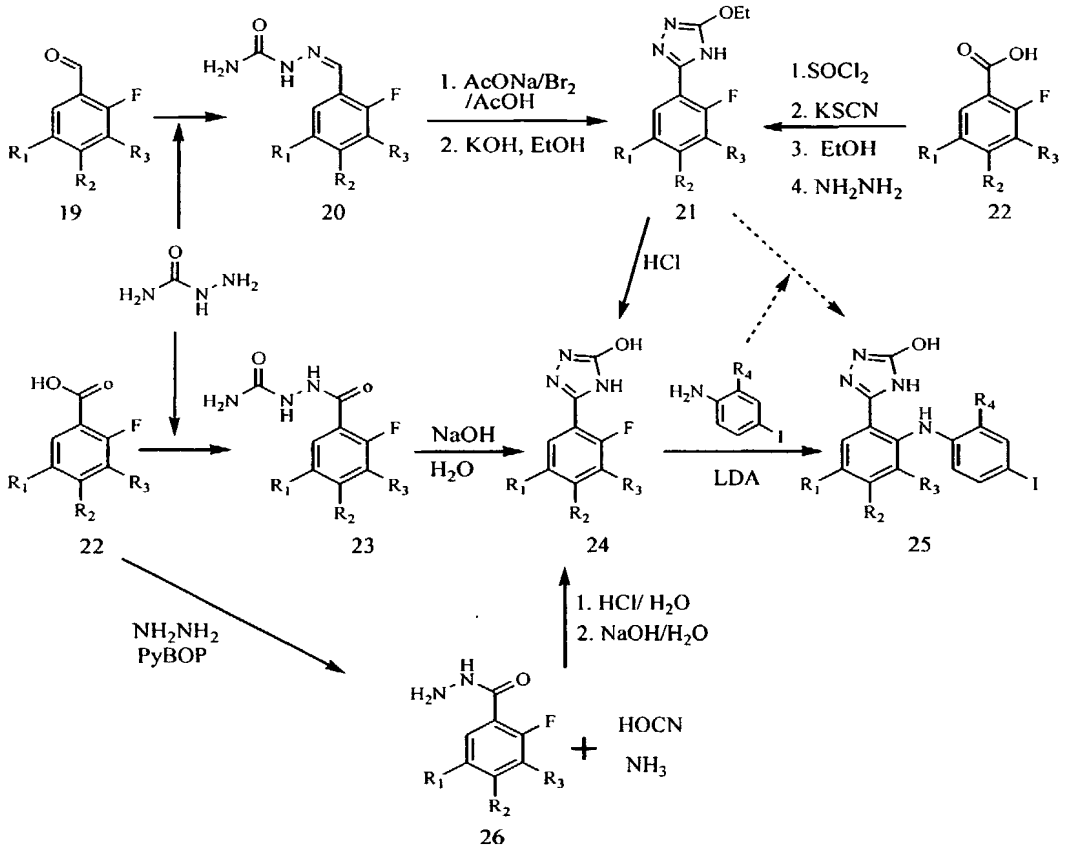


14 15

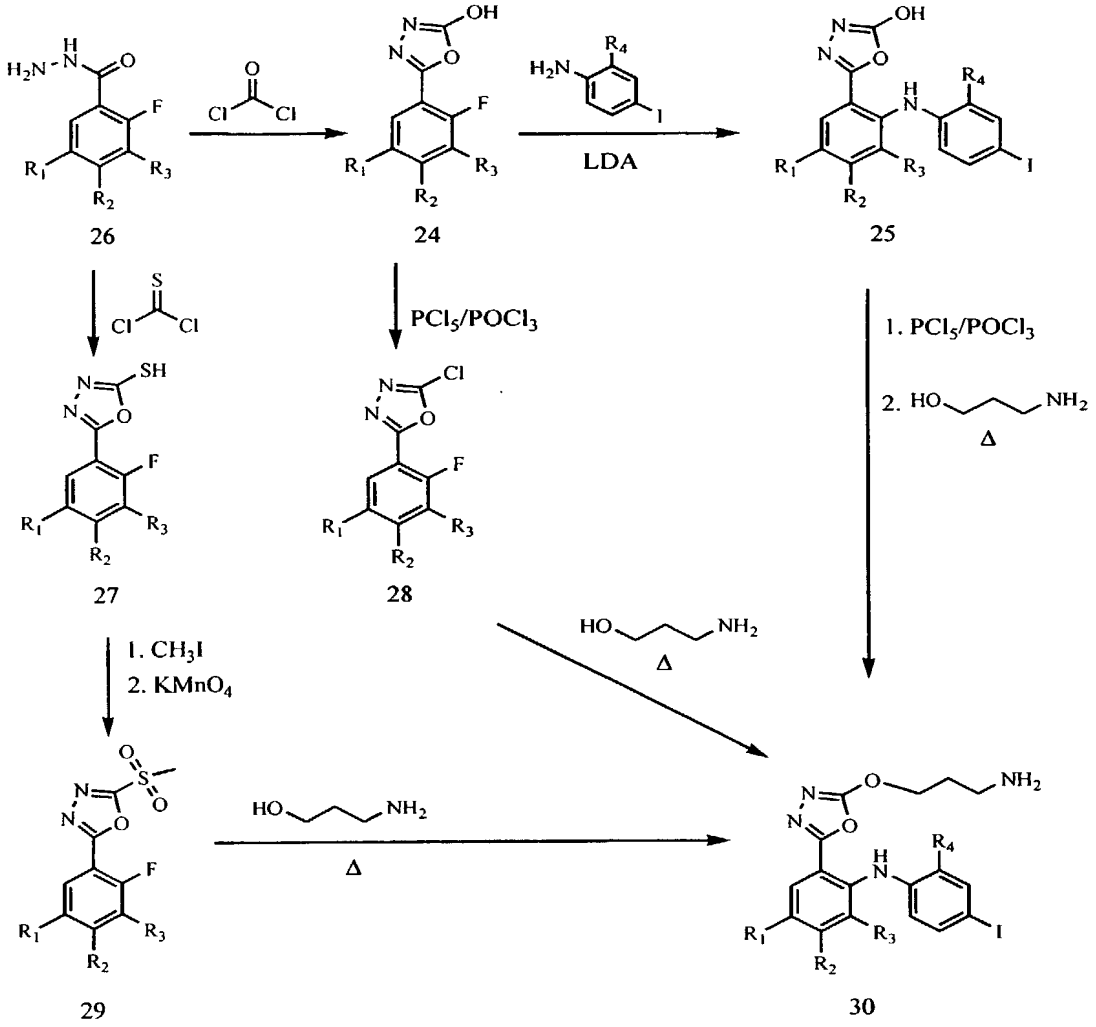


16 17 18

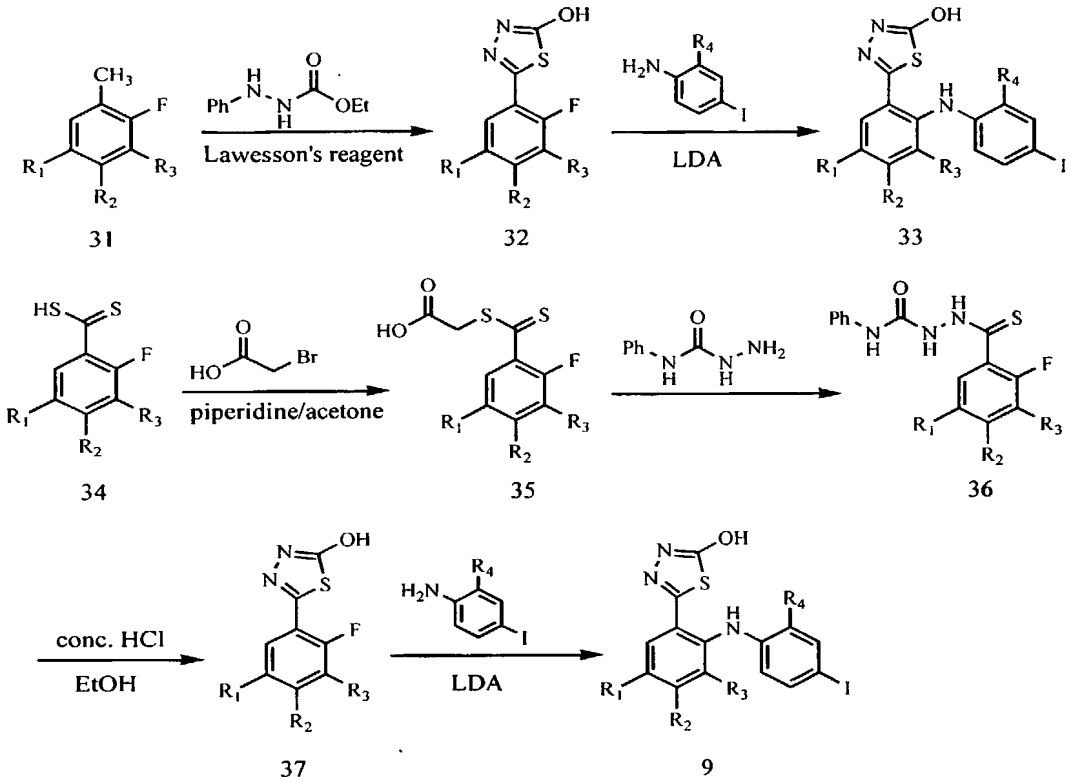
Scheme 3


1. AcONa/Br2 /AcOH
2. KOH, EtOH
1.SOCl2
2. KSCN
3. EtOH
4. NH2NH2
HCl
NaOH
H2O
LDA
NH2NH2
PyBOP
1. HCl/ H2O
2. NaOH/H2O
HOCN
NH3
19
20
21
22
22
23
24
25
26

Scheme 4


26
24
25
LDA
PCl5/POCl3
1. PCl5/POCl3
2. HO NH2
Δ
27
28
1. CH3I
2. KMnO4
HO NH2
Δ
HO NH2
Δ
29
30

Scheme 5

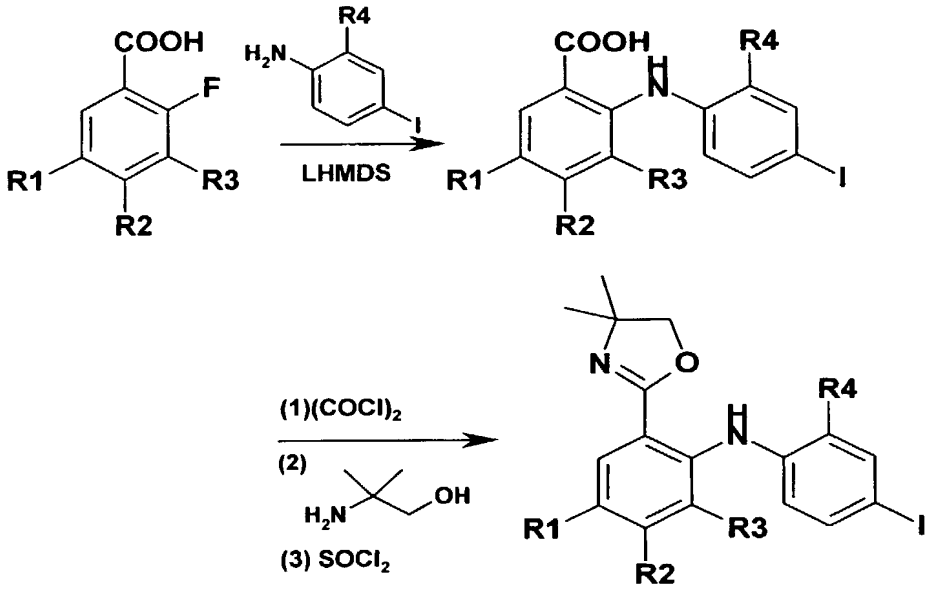


31 32 33

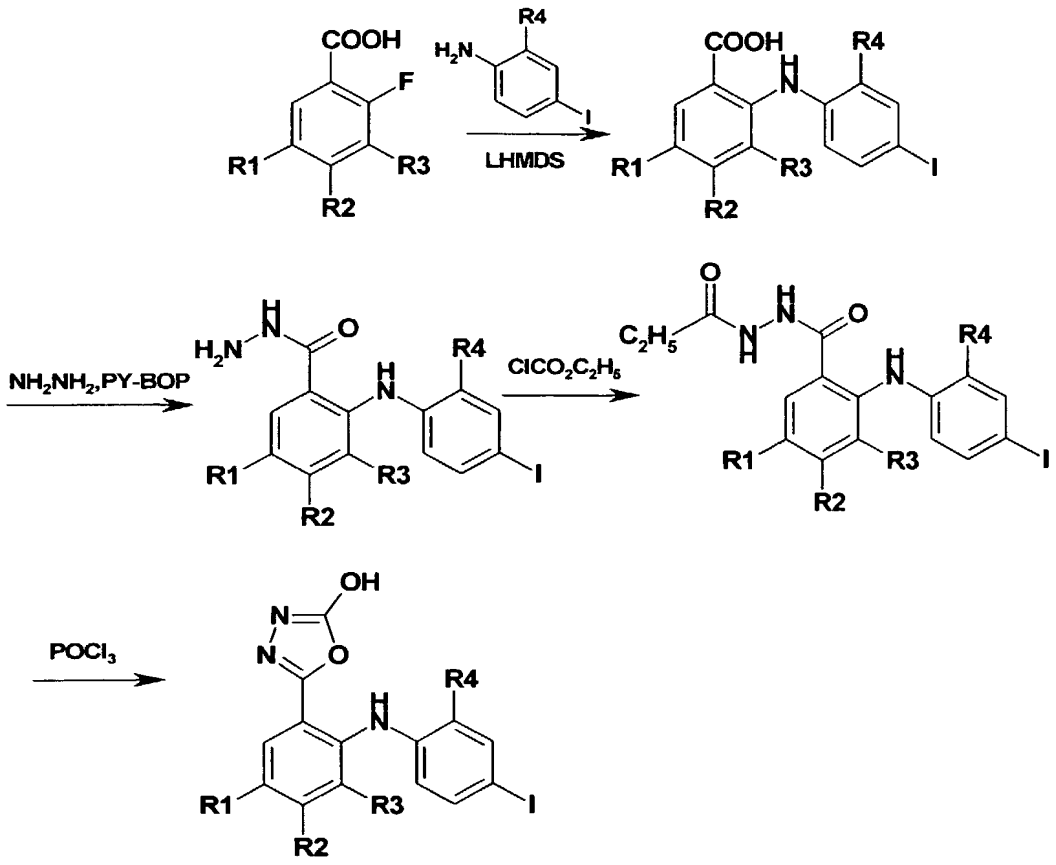
34 35 36

37 9

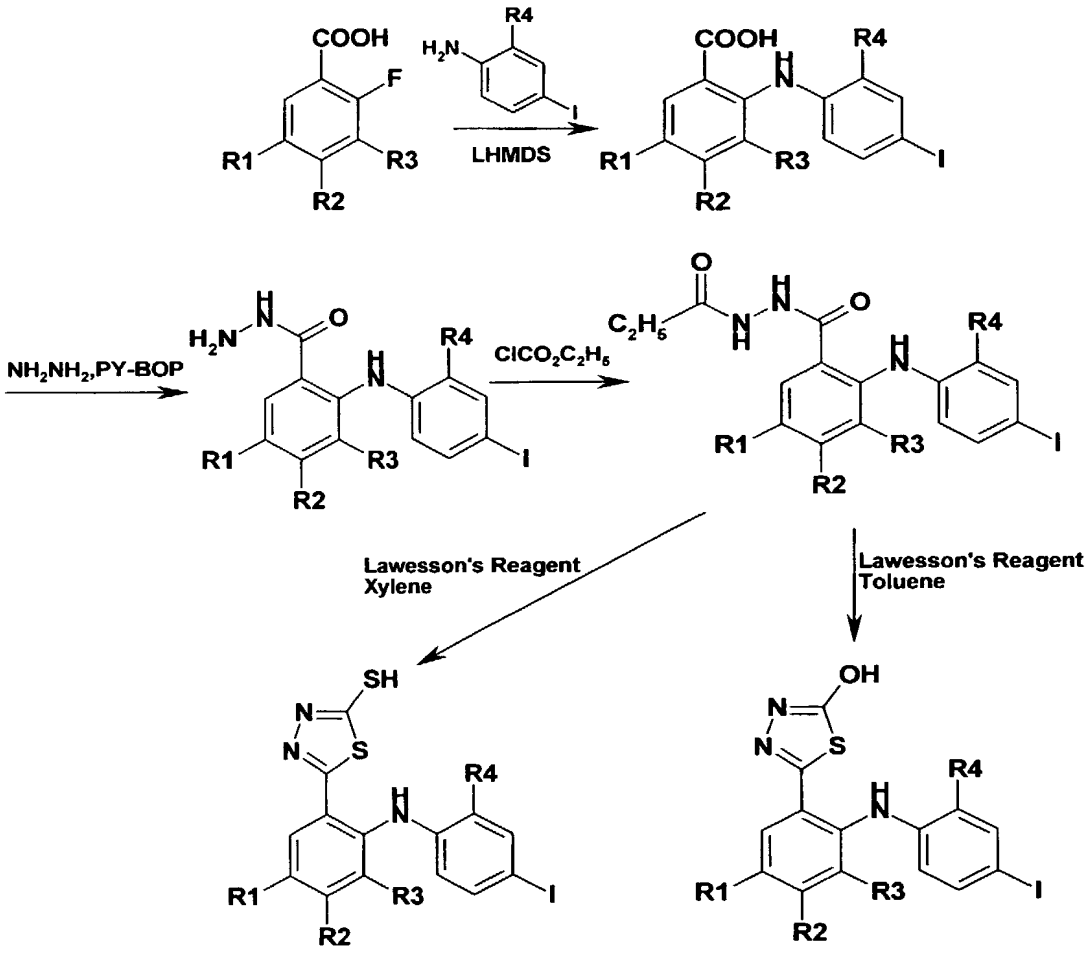
Scheme 6


COOH
F
R1
R3
R2
R4
H2N
I
LHMDS
COOH
R4
N
H
R1
R3
R2
I
(1)(COCl)2
(2)
H2N
OH
(3) SOCl2
N
O
R4
N
H
R1
R3
R2
I

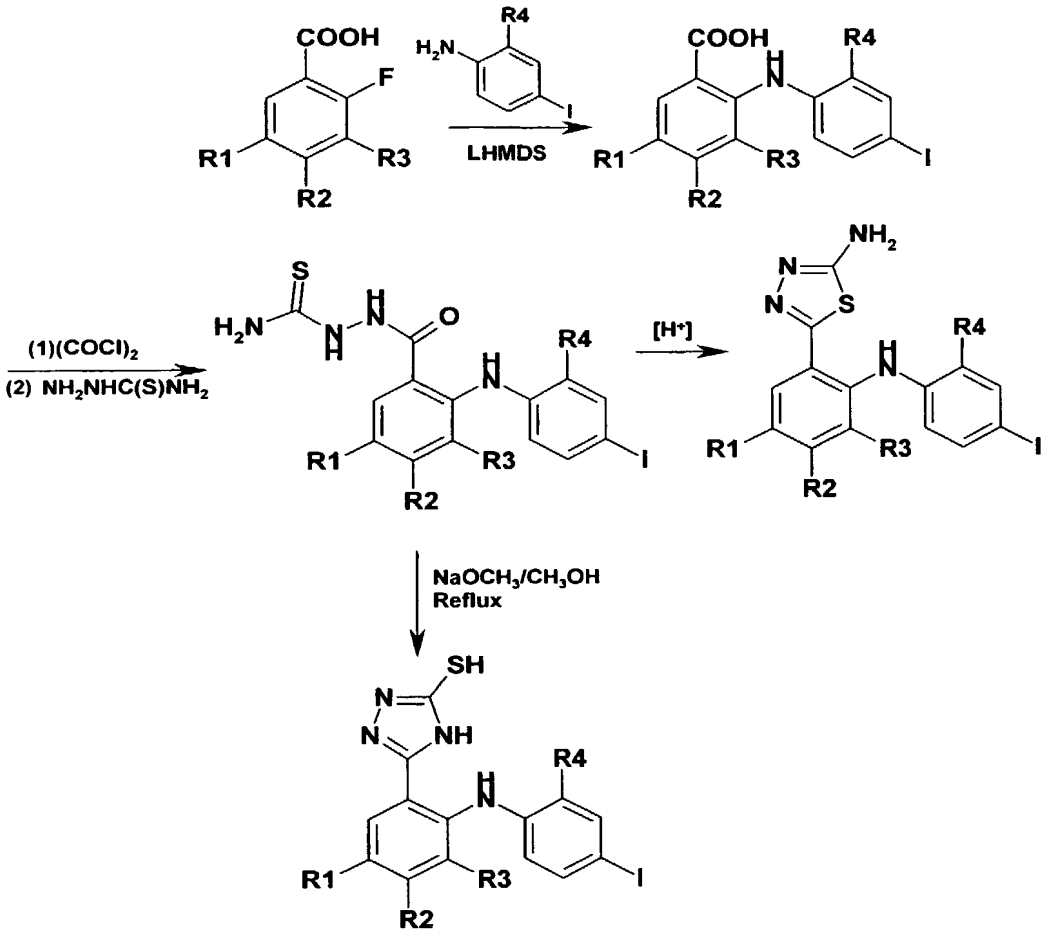
Scheme 7


COOH
F
R1
R3
R2
R4
H2N
I
LHMDS
NH2NH2,PY-BOP
ClCO2C2H5
C2H5
O
N
H
OH
POCl3

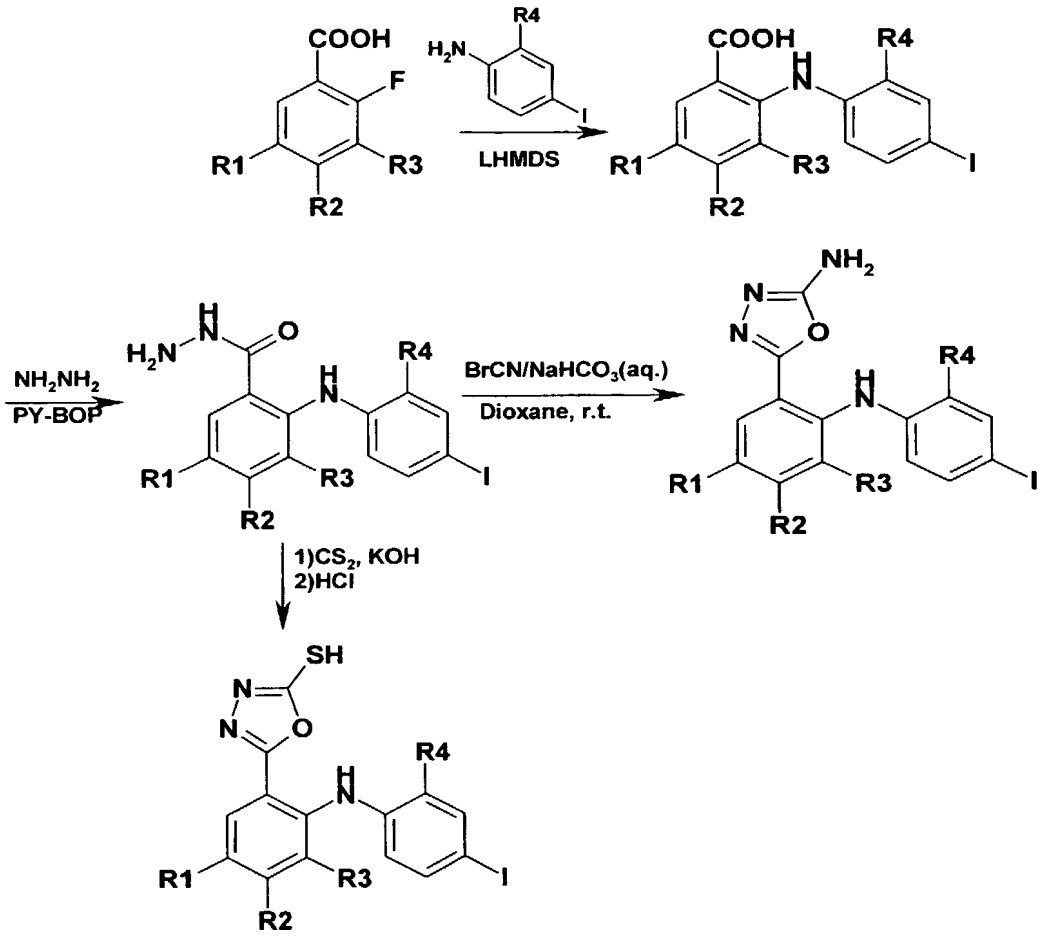
Scheme 8


COOH
F
R1
R3
R2
R4
H2N
I
LHMDS
COOH
R4
N
H
R1
R3
I
R2
NH2NH2,PY-BOP
H2N
N
H
O
R4
ClCO2C2H5
C2H5
Lawesson's Reagent
Xylene
Lawesson's Reagent
Toluene
SH
OH
S

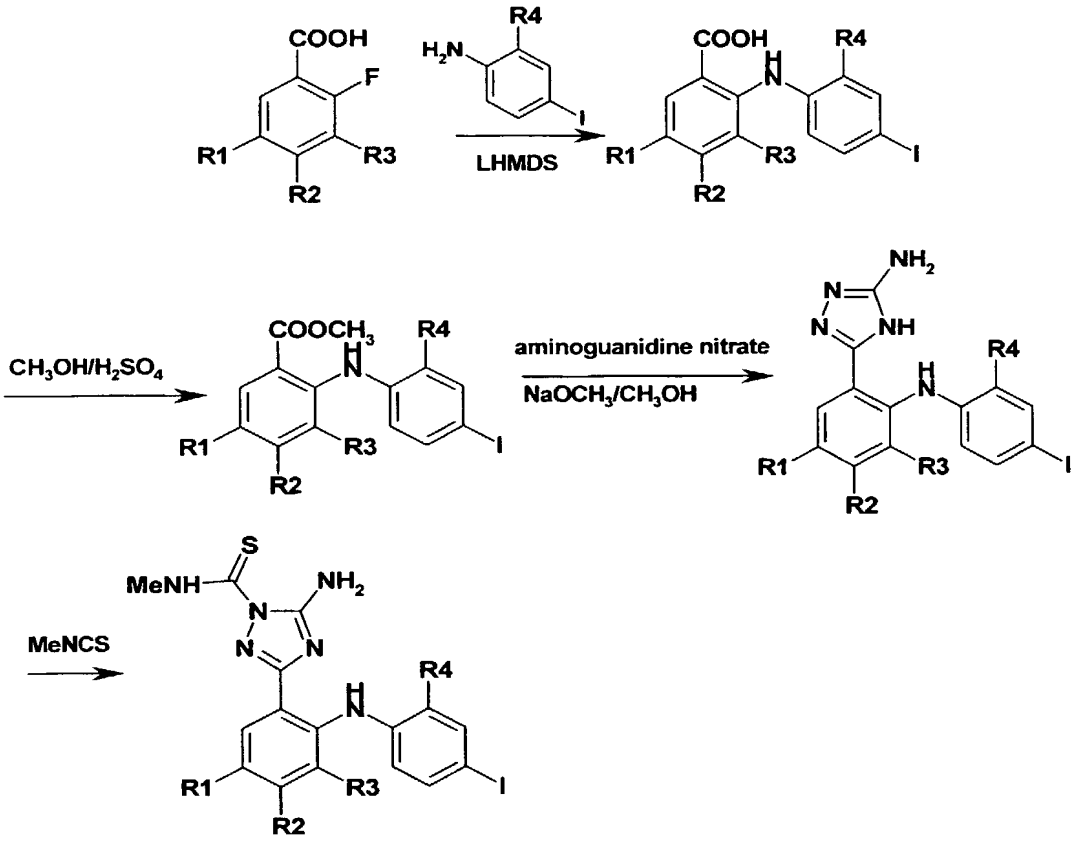
Scheme 9


COOH
F
R1
R3
R2
R4
H2N
I
LHMDS
COOH
R4
N
H
R1
R3
R2
I
(1)(COCl)2
(2) NH2NHC(S)NH2
S
H2N
N
H
N
H
O
R4
N
H
R1
R3
R2
I
[H+]
NH2
N
N
S
R4
N
H
R1
R3
R2
I
NaOCH3/CH3OH
Reflux
SH
N
N
NH
R4
N
H
R1
R3
R2
I

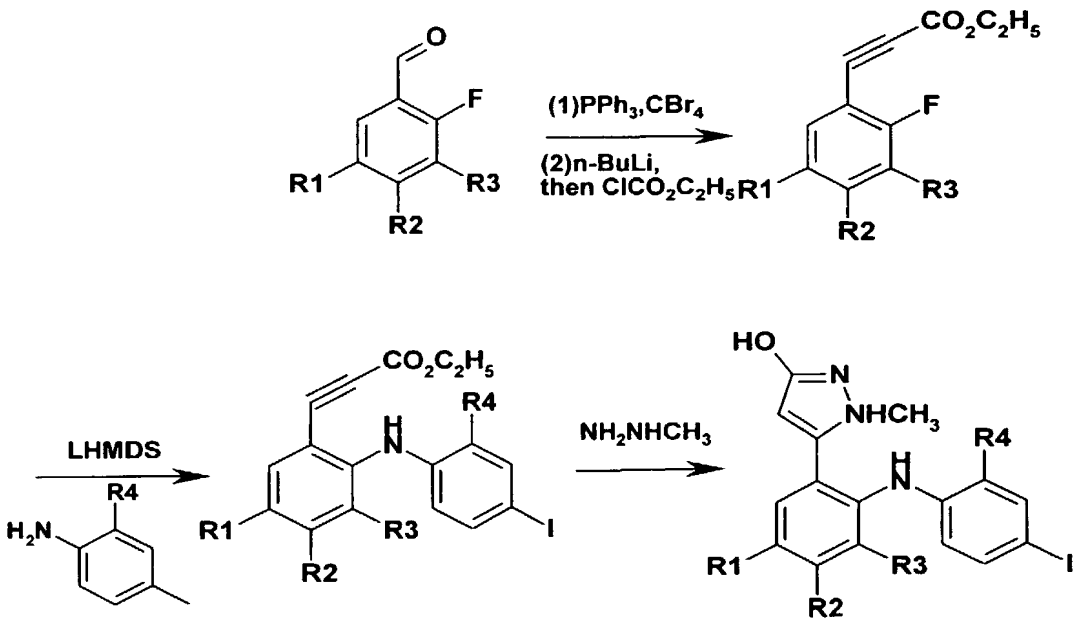
Scheme 10


COOH
F
R1
R3
R2
R4
H2N
I
LHMDS
NH2NH2
PY-BOP
BrCN/NaHCO3(aq.)
Dioxane, r.t.
NH2
1)CS2, KOH
2)HCl
SH

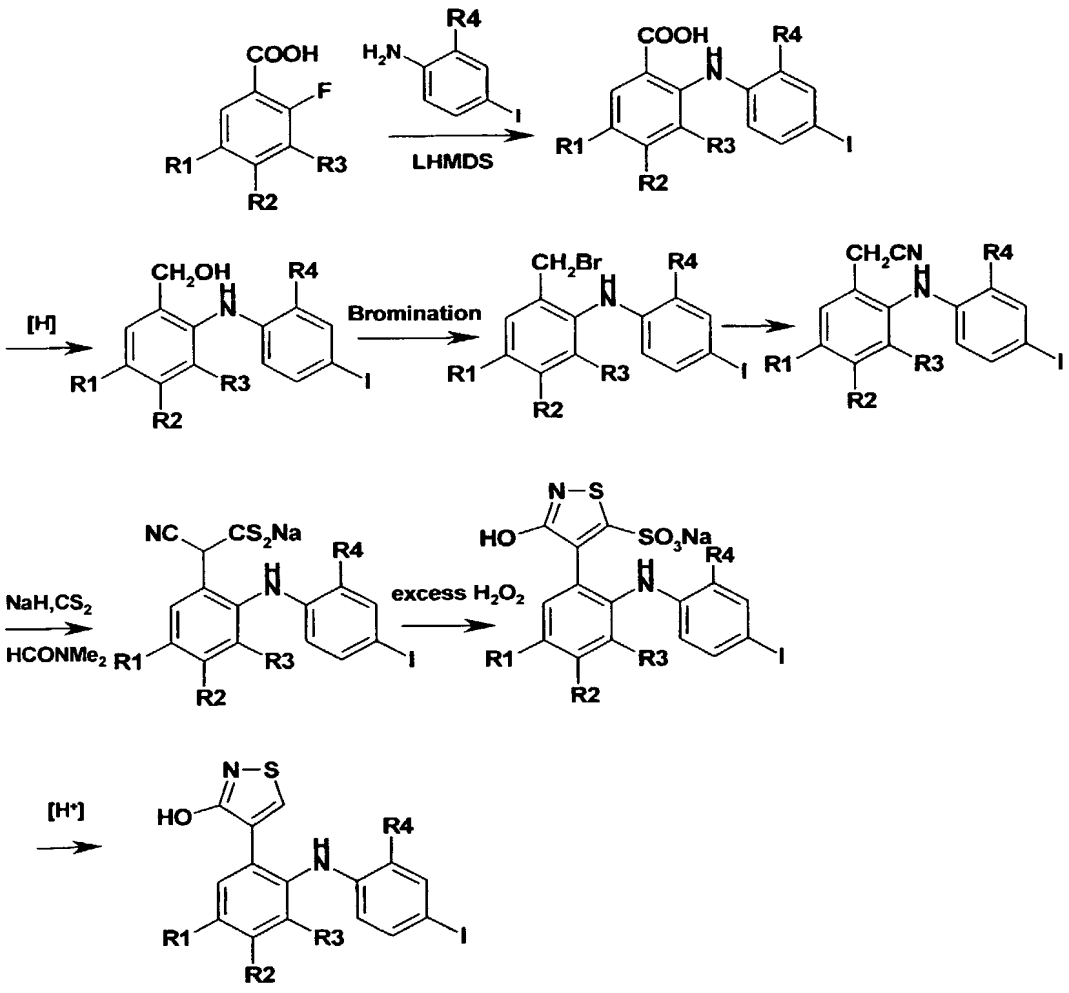
Scheme 11


COOH
F
R1
R3
R2
R4
H_2N
I
LHMDS
COOH
R4
H
N
R1
R3
I
R2
CH_3OH/H_2SO_4
$COOCH_3$
R4
H
N
R1
R3
I
R2
aminoguanidine nitrate
$NaOCH_3/CH_3OH$
NH_2
N
N
NH
R4
H
N
R1
R3
I
R2
MeNCS
S
MeNH
NH_2
N
N
N
R4
H
N
R1
R3
I
R2

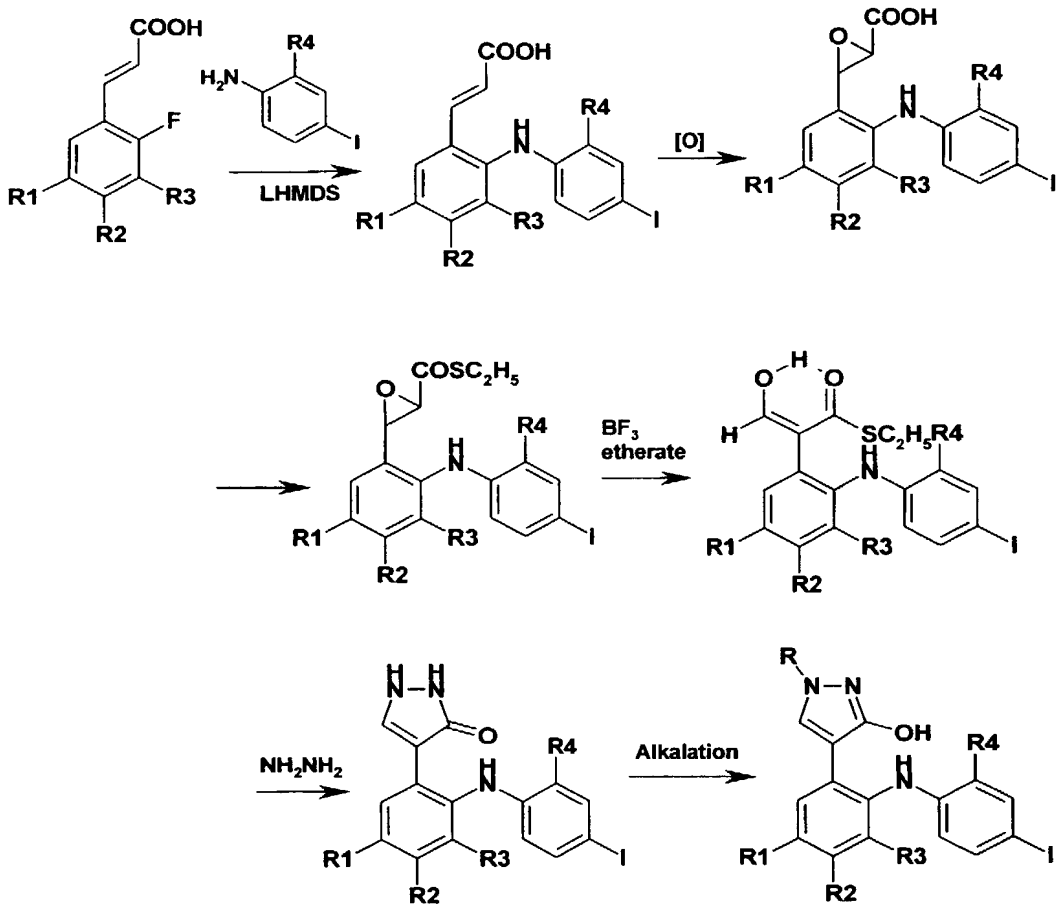
Scheme 12


O
F
R1
R3
R2
(1)PPh3,CBr4
(2)n-BuLi,
then ClCO2C2H5
CO2C2H5
F
R1
R3
R2
LHMDS
R4
H2N
CO2C2H5
R4
H
N
R1
R3
R2
I
NH2NHCH3
HO
N
NHCH3
R4
H
N
R1
R3
R2
I

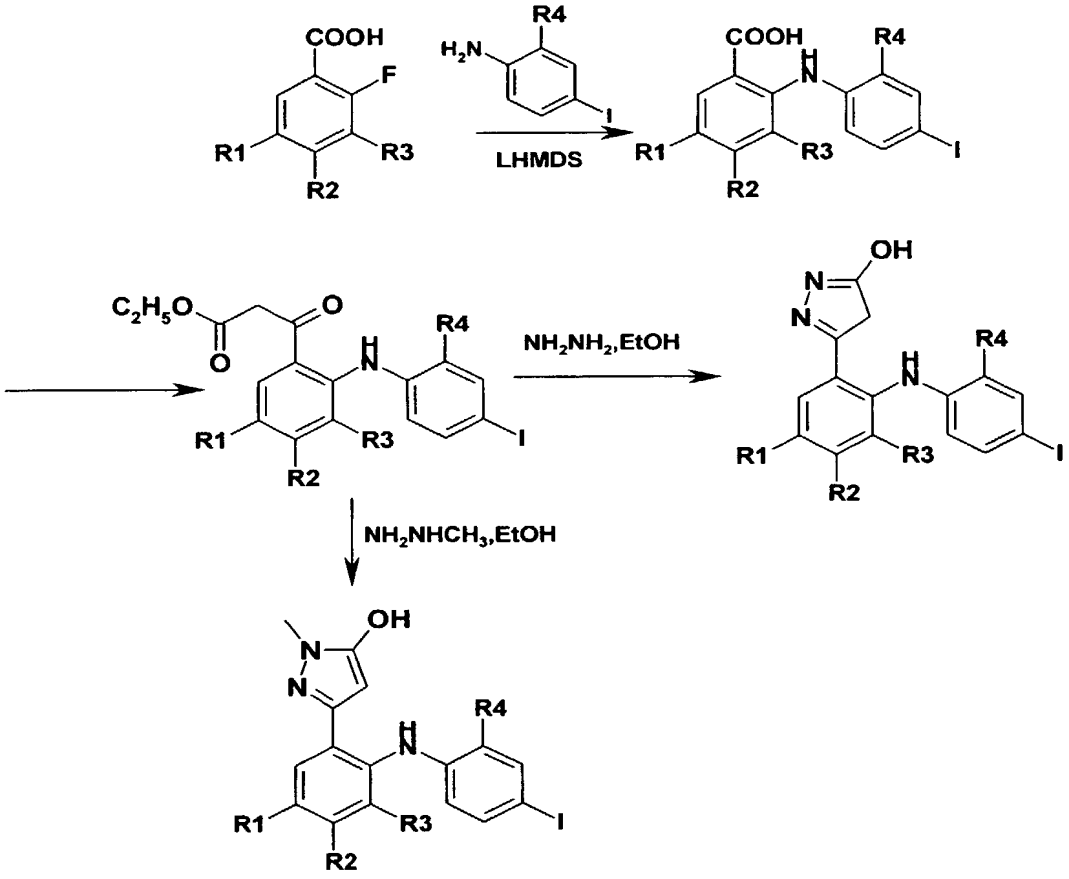
Scheme 13


COOH
F
R1
R3
R2
R4
H_2N
I
LHMDS
COOH
R4
N
H
R1
R3
R2
I
[H]
CH_2OH
R4
N
H
R1
R3
R2
I
Bromination
CH_2Br
R4
N
H
R1
R3
R2
I
CH_2CN
R4
N
H
R1
R3
R2
I
NaH,CS_2
$HCONMe_2$
NC
CS_2Na
R4
N
H
R1
R3
R2
I
excess H_2O_2
N–S
HO
SO_3Na
R4
N
H
R1
R3
R2
I
[H+]
N–S
HO
R4
N
H
R1
R3
R2
I

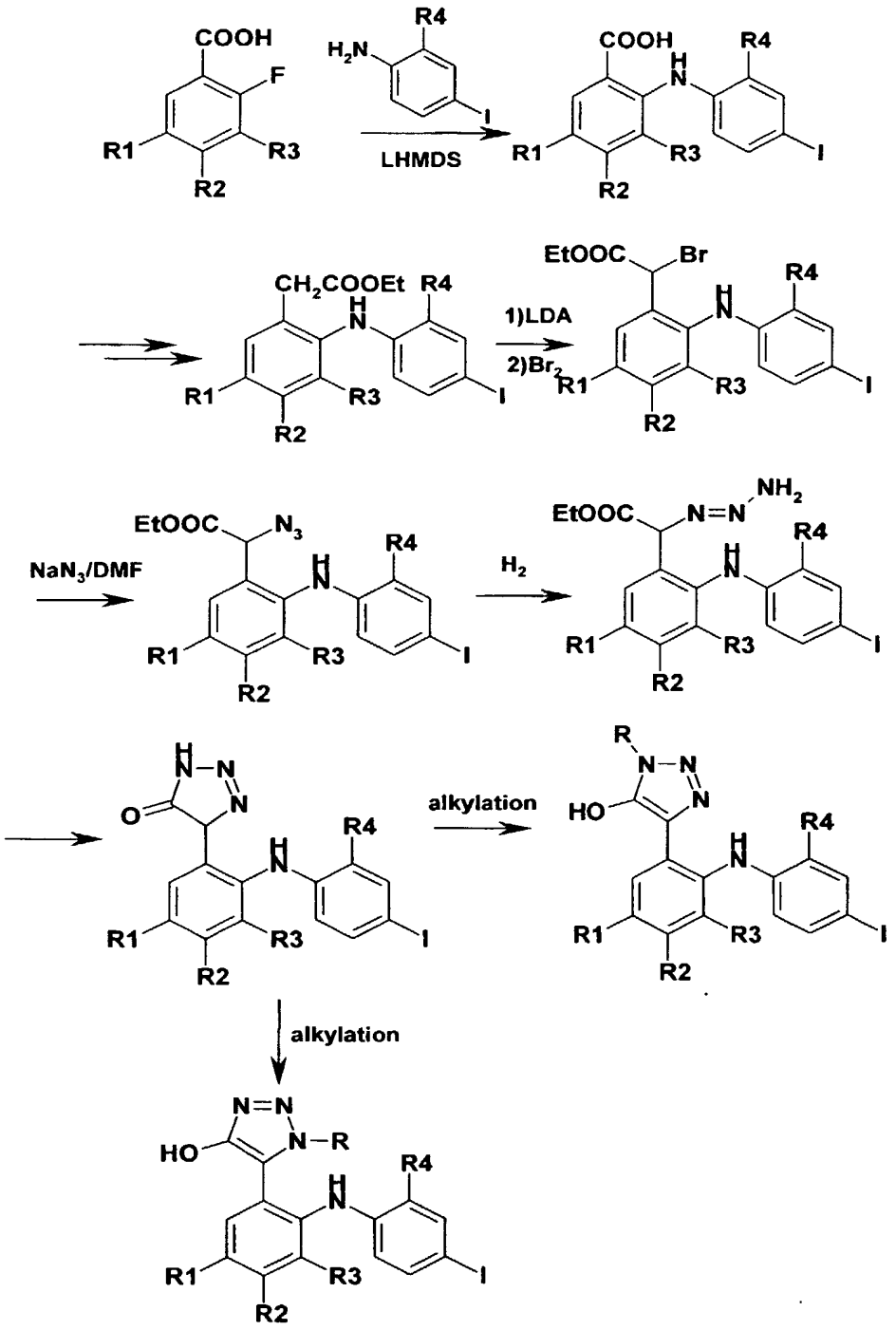
Scheme 14


COOH
R4
H_2N
I
F
R1
R3
R2
LHMDS
[O]
O
H
N
$COSC_2H_5$
BF_3
etherate
SC_2H_5
NH_2NH_2
Alkalation
OH
R

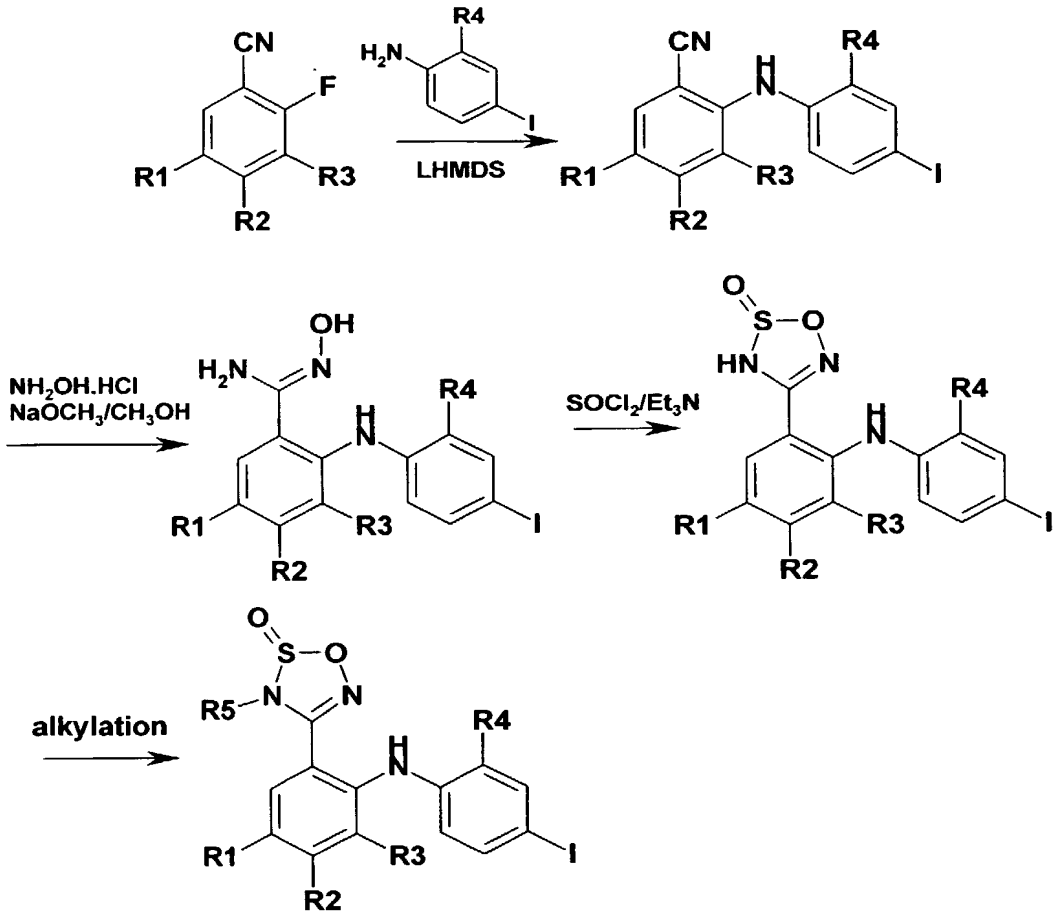
Scheme 15


COOH
F
R1
R3
R2
R4
H_2N
I
LHMDS
COOH
H
N
R4
R1
R3
R2
I
C_2H_5O
O
O
R4
H
N
R1
R3
R2
I
NH_2NH_2,EtOH
OH
N
N
R4
H
N
R1
R3
R2
I
NH_2NHCH_3,EtOH
OH
N
N
R4
H
N
R1
R3
R2
I

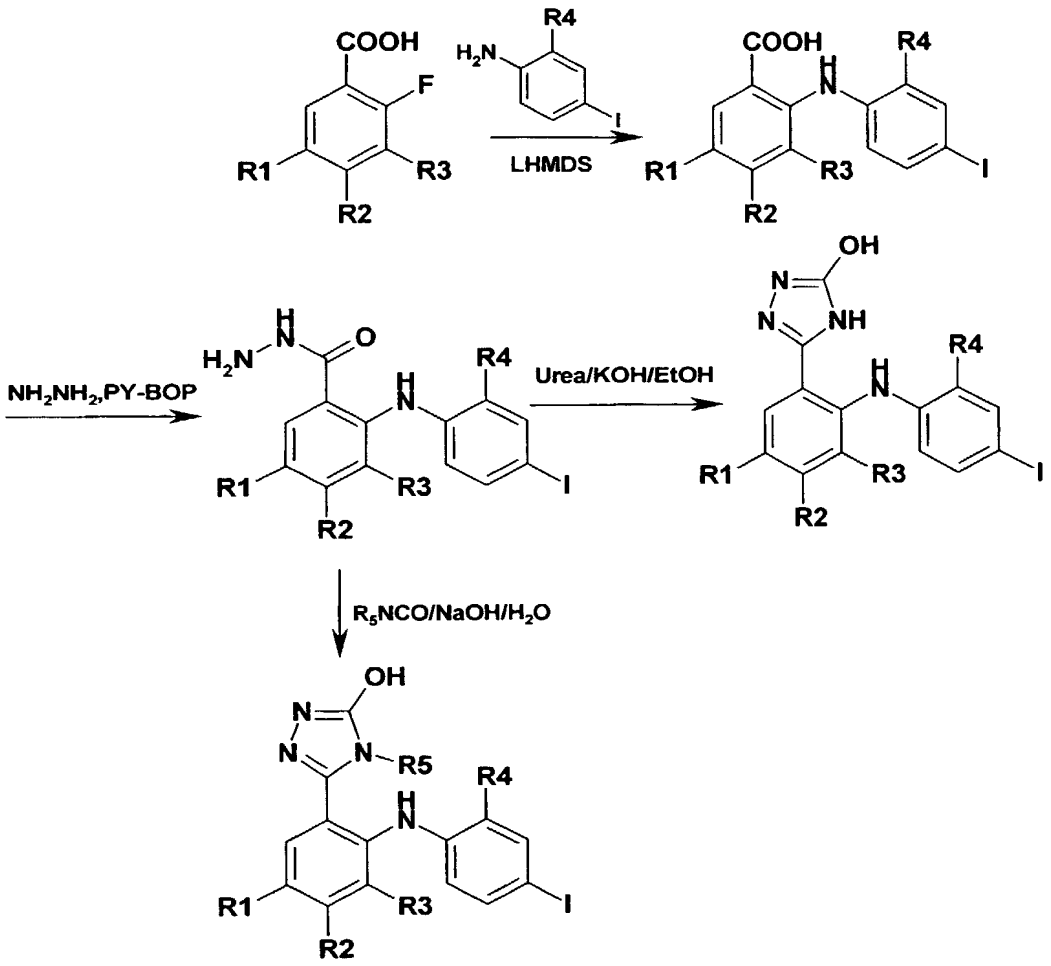
Scheme 16


COOH
F
R1
R3
R2
R4
H_2N
I
LHMDS
H
N
CH_2COOEt
1)LDA
2)Br_2
EtOOC
Br
NaN_3/DMF
N_3
H_2
NH_2
N=N
O
alkylation
HO
R

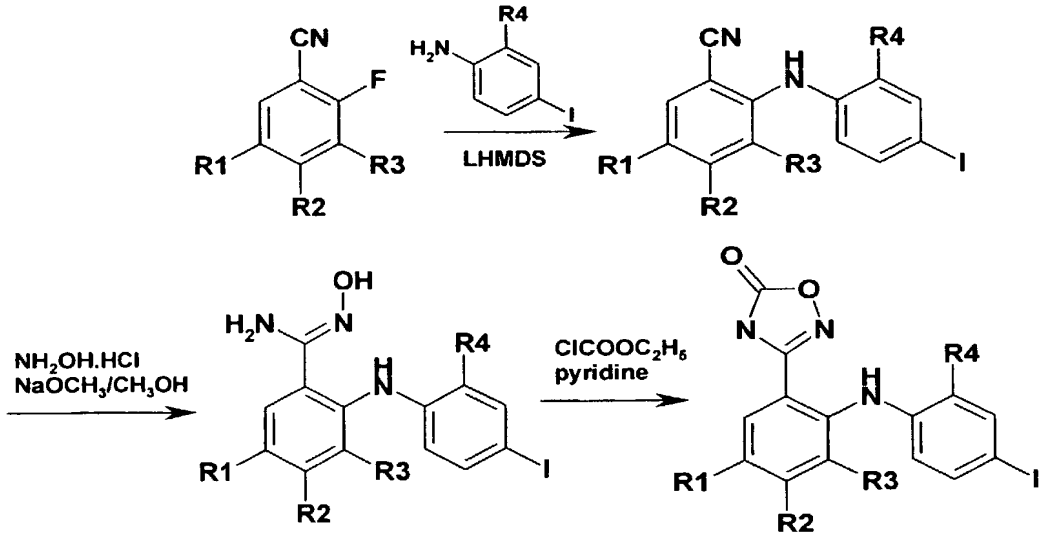
Scheme 17


CN
F
R1
R3
R2
H2N
R4
I
LHMDS
NH2OH.HCl
NaOCH3/CH3OH
OH
SOCl2/Et3N
alkylation
R5
O
S
HN
N

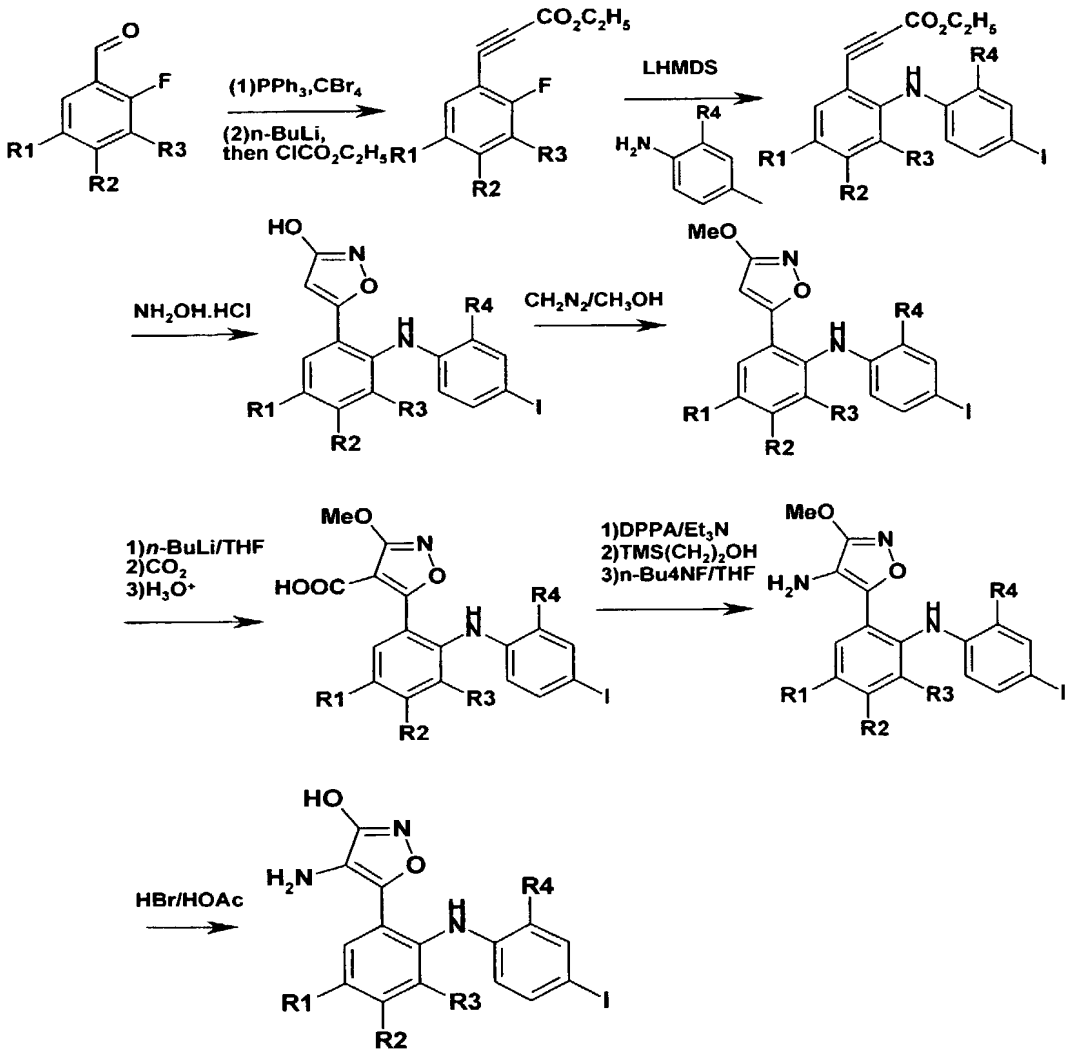
Scheme 18


COOH
F
R1
R3
R2
R4
H_2N
I
LHMDS
COOH
R4
N
H
R1
R3
R2
I
OH
N
N
NH
R4
H
N
R1
R3
R2
I
Urea/KOH/EtOH
NH_2NH_2,PY-BOP
H_2N
N
H
O
R4
H
N
R1
R3
R2
I
$R_5NCO/NaOH/H_2O$
OH
N
N
N
R5
R4
H
N
R1
R3
R2
I

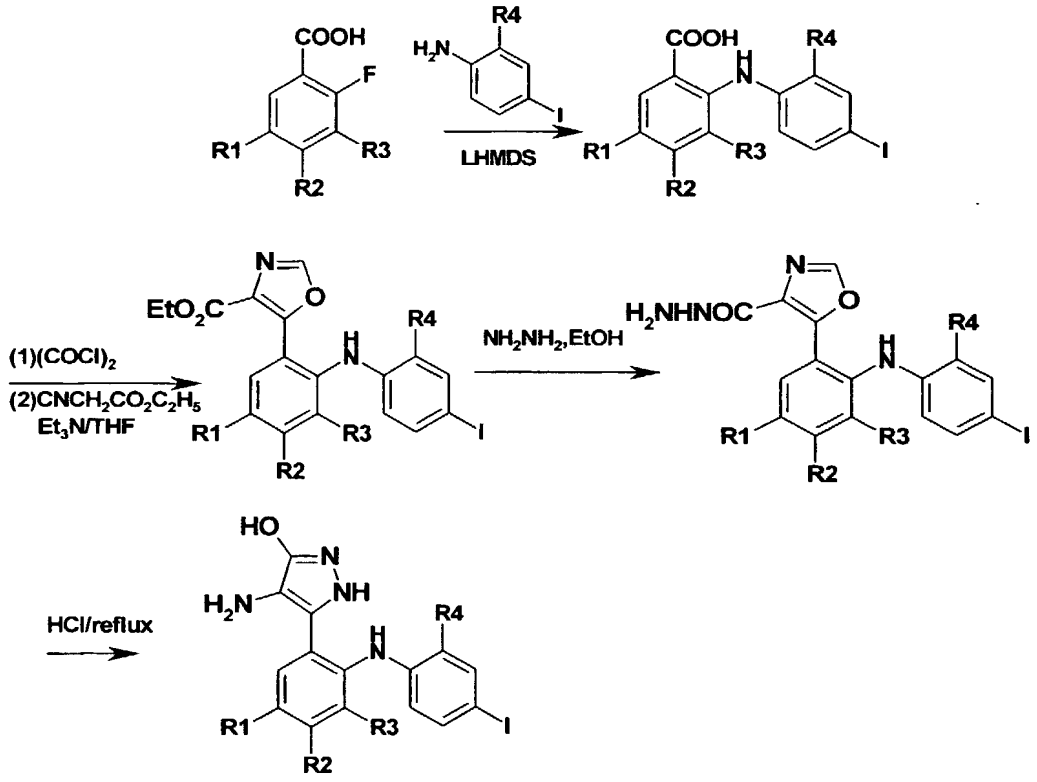
Scheme 19


CN
F
R1
R3
R2
R4
H2N
I
LHMDS
CN
R4
H
N
R1
R3
I
R2
NH2OH.HCl
NaOCH3/CH3OH
OH
H2N
N
R4
H
N
R1
R3
I
R2
ClCOOC2H5
pyridine
O
O
N
N
R4
H
N
R1
R3
I
R2

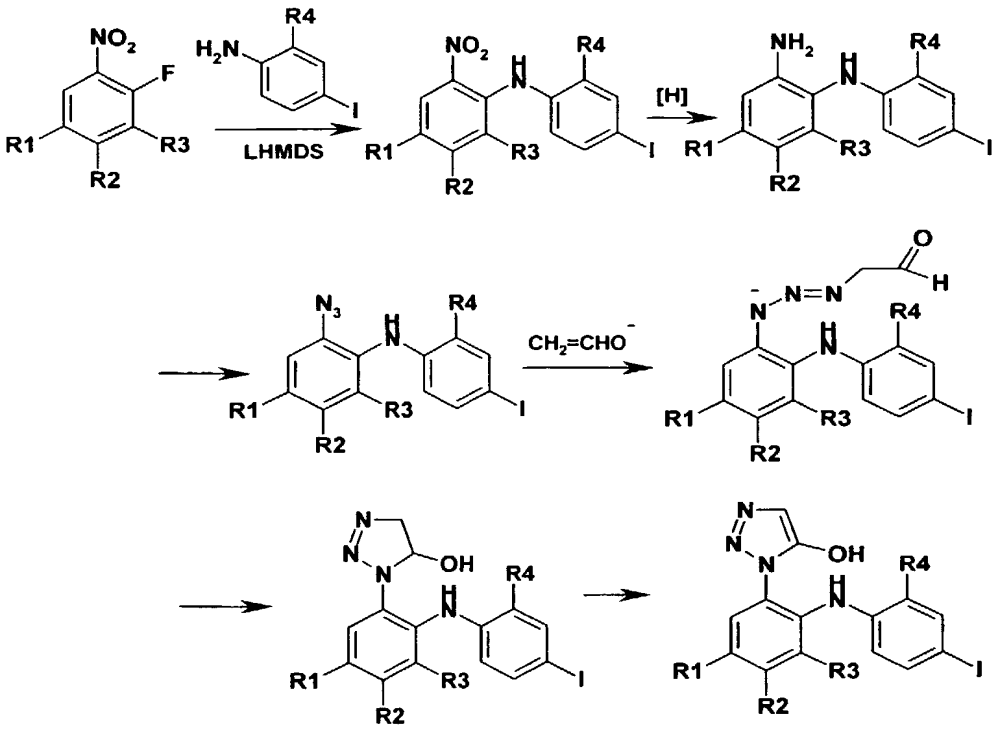
Scheme 20


(1)PPh3,CBr4
(2)n-BuLi,
then ClCO2C2H5
LHMDS
NH2OH.HCl
CH2N2/CH3OH
1)n-BuLi/THF
2)CO2
3)H3O+
1)DPPA/Et3N
2)TMS(CH2)2OH
3)n-Bu4NF/THF
HBr/HOAc

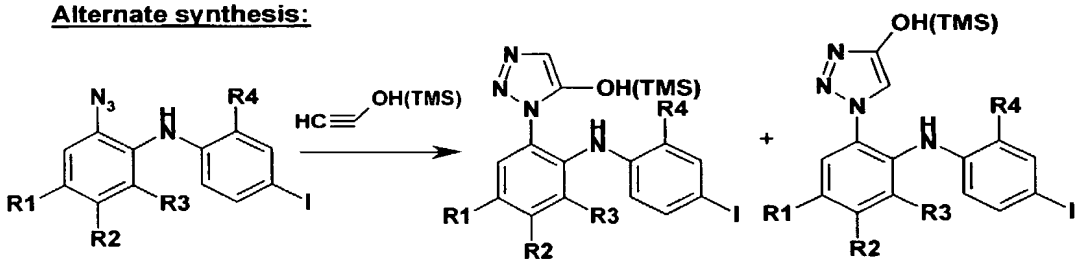
Scheme 21


COOH
F
R1
R3
R2
R4
H2N
I
LHMDS
COOH
R4
N
H
R1
R3
R2
I
N
O
EtO2C
(1)(COCl)2
(2)CNCH2CO2C2H5
Et3N/THF
NH2NH2,EtOH
H2NHNOC
HO
N
NH
H2N
HCl/reflux

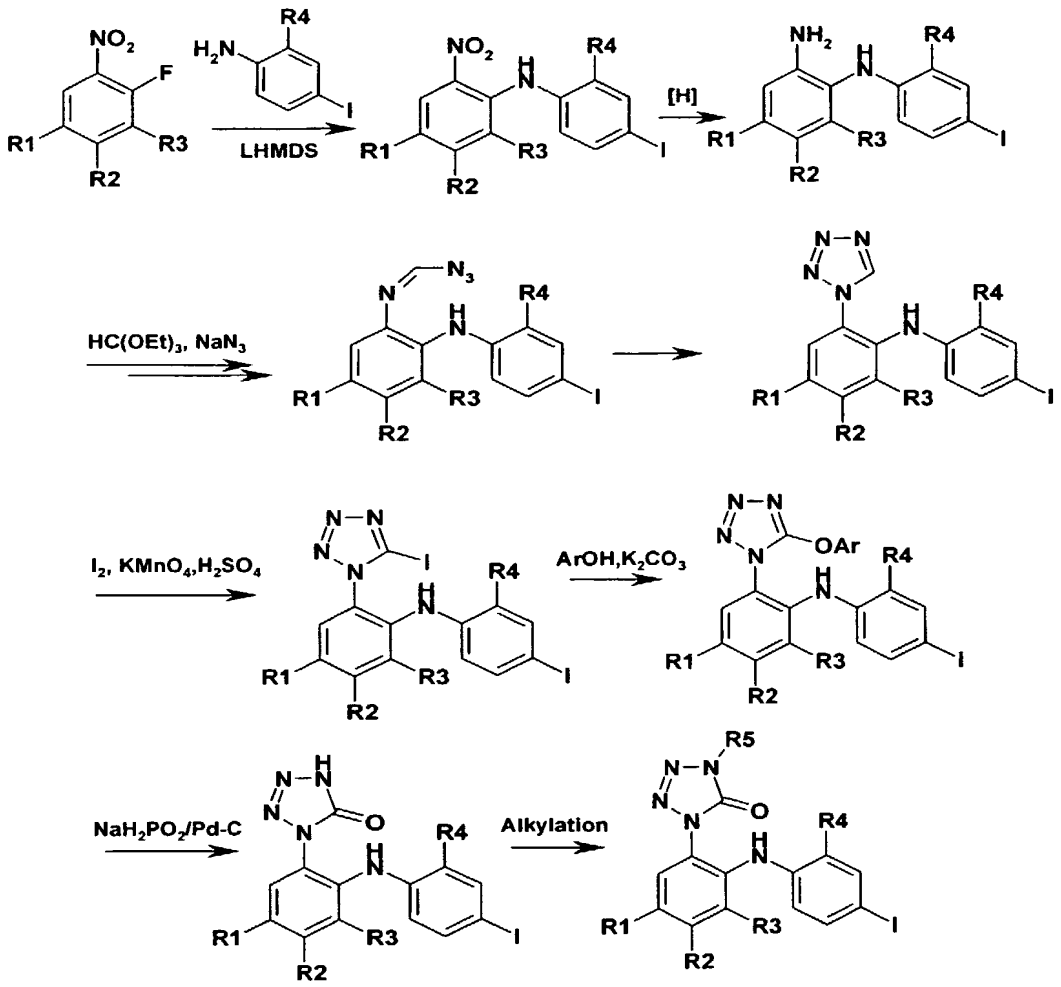
Scheme 22



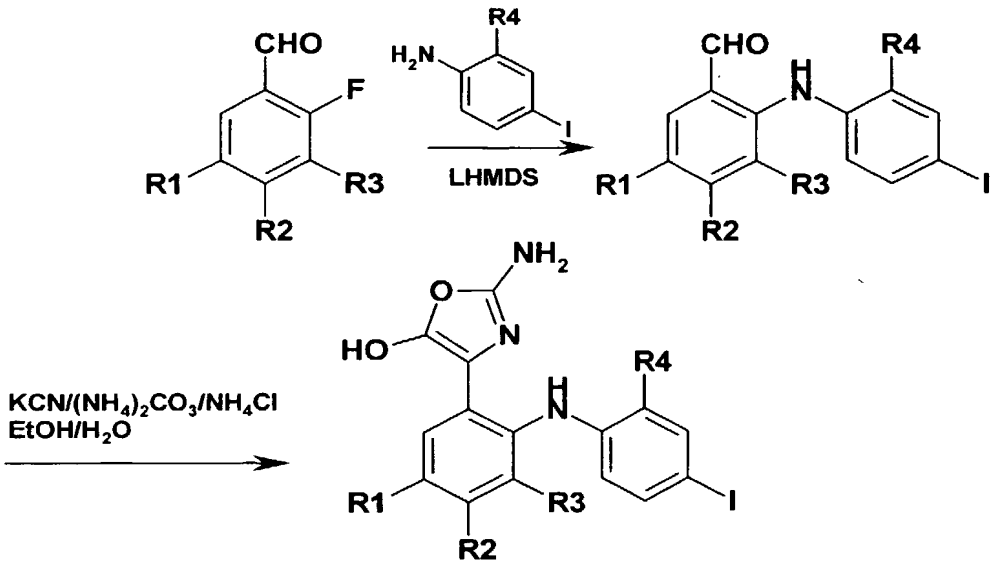
Alternate synthesis:



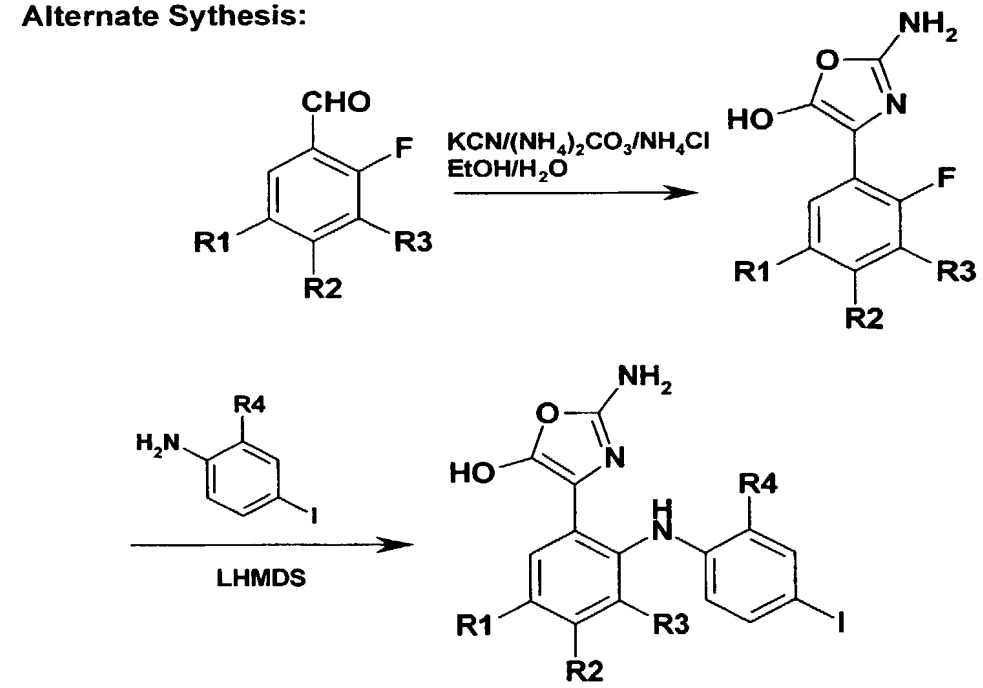
Scheme 23


NO2
F
R1
R3
R2
H2N
R4
I
LHMDS
NO2
H
N
R4
[H]
NH2
HC(OEt)3, NaN3
N3
I2, KMnO4,H2SO4
ArOH,K2CO3
OAr
NaH2PO2/Pd-C
Alkylation
R5
O

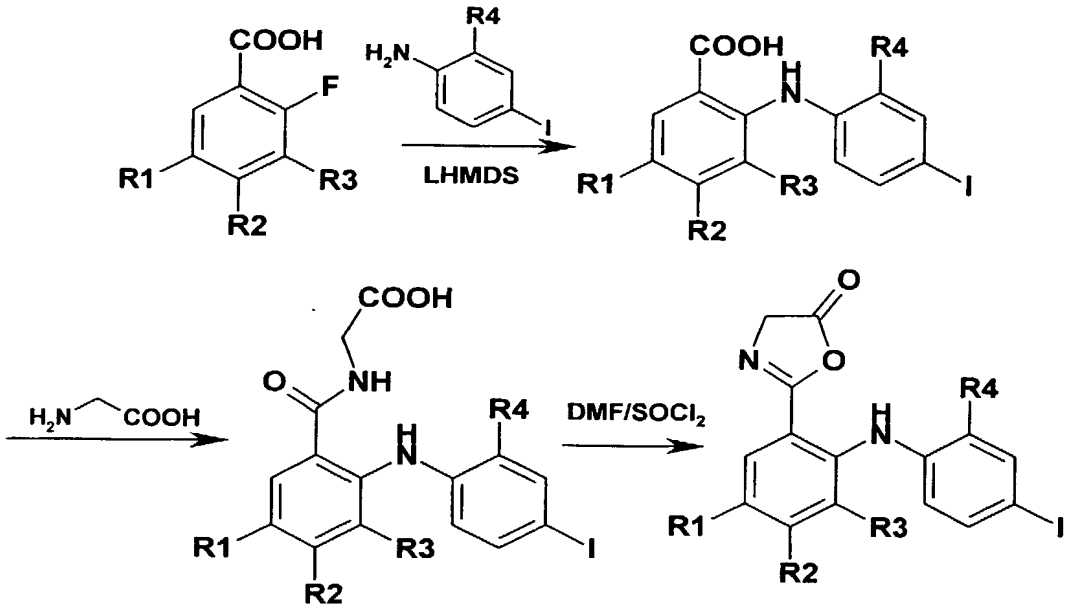
Scheme 24



Alternate Sythesis:



Scheme 25


COOH
F
R1
R3
R2
H2N
R4
I
LHMDS
COOH
R4
N
H
R1
R3
R2
I
H2N
COOH
COOH
O
NH
R4
N
H
R1
R3
R2
I
DMF/SOCl2
O
N
O
R4
N
H
R1
R3
R2
I

D. Uses

The disclosed compositions are useful as both prophylactic and therapeutic treatments for diseases or conditions relating to chronic pain, including neuropathic pain, as provided in the Summary section, as well as diseases or conditions modulated by the MEK cascade. For example, in one embodiment, the disclosed method relates to postoperative pain, phantom limb pain, burn pain, gout, trigeminal neuralgia, acute herpetic and postherpetic pain, causalgia, diabetic neuropathy, plexus avulsion, neuroma, vasculitis, crush injury, constriction injury, tissue injury, post-surgical pain, arthritis pain, or limb amputation

For example, local injuries can be treated with local or topical administration. Chronic pain affecting the entire body, such as diabetic neuropathy can be treated with systemic administration (injection or orally) of a disclosed composition. Treatment for chronic pain (e.g., post-operative pain) confined to the lower body can be administered centrally, e.g., epidurally. Formulations and methods of administration can include the use of more than one MEK inhibitor, or a combination of a MEK inhibitor and another pharmaceutical agent, such as an anti-inflammatory, analgesic, muscle relaxing, or anti-infective agent. Preferred routes of administration are oral, intrathecal or epidural, subcutaneous, intravenous, intramuscular, and, for non-human mammals, intraplantar, and are preferably epidural.

1. Dosages

Those skilled in the art will be able to determine, according to known methods, the appropriate dosage for a patient, taking into account factors such as age, weight, general health, the type of pain requiring treatment, and the presence of other medications. In general, an effective amount will be between 0.1 and 1000 mg/kg per day, preferably between 1 and 300 mg/kg body weight, and daily dosages will be between 10 and 5000 mg for an adult subject of normal weight. Commercially available capsules or other

formulations (such as liquids and film-coated tablets) of 100 mg, 200 mg, 300 mg, or 400 mg can be administered according to the disclosed methods.

2. Formulations

Dosage unit forms include tablets, capsules, pills, powders, granules, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers adapted for subdivision into individual doses. Dosage unit forms can also be adapted for various methods of administration, including controlled release formulations, such as subcutaneous implants. Administration methods include oral, rectal, parenteral (intravenous, intramuscular, subcutaneous), intracisternal, intravaginal, intraperitoneal, intravesical, local (drops, powders, ointments, gels, or cream), and by inhalation (a buccal or nasal spray).

Parenteral formulations include pharmaceutically acceptable aqueous or nonaqueous solutions, dispersion, suspensions, emulsions, and sterile powders for the preparation thereof. Examples of carriers include water, ethanol, polyols (propylene glycol, polyethylene glycol), vegetable oils, and injectable organic esters such as ethyl oleate. Fluidity can be maintained by the use of a coating such as lecithin, a surfactant, or maintaining appropriate particle size. Carriers for solid dosage forms include (a) fillers or extenders, (b) binders, (c) humectants, (d) disintegrating agents, (e) solution retarders, (f) absorption acccelerators, (g) adsorbants, (h) lubricants, (i) buffering agents, and (j) propellants.

Compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents; antimicrobial agents such as parabens, chlorobutanol, phenol, and sorbic acid; isotonic agents such as a sugar or sodium chloride; absorption-prolonging agents such as aluminum monostearate and gelatin; and absorption-enhancing agents.

3. Related compounds

The invention provides the disclosed compounds and closely related, pharmaceutically acceptable forms of the disclosed compounds, such as salts, esters, amides, hydrates or solvated forms thereof; masked or protected forms; and racemic mixtures, or enantiomerically or optically pure forms.

Pharmaceutically acceptable salts, esters, and amides include carboxylate salts (e.g., C_{1-8} alkyl, cycloalkyl, aryl, heteroaryl, or non-aromatic heterocyclic), amino acid addition salts, esters, and amides which are within a reasonable benefit/risk ratio, pharmacologically effective, and suitable for contact with the tissues of patients without undue toxicity, irritation, or allergic response. Representative salts include hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactiobionate, and laurylsulfonate. These may include alkali metal and alkali earth cations such as sodium, potassium, calcium, and magnesium, as well as non-toxic ammonium, quaternary ammonium, and amine cations such as tetramethyl ammonium, methylamine, trimethylamine, and ethylamine. See, for example, S.M. Berge, et al., "Pharmaceutical Salts," *J. Pharm. Sci.,* 1977, 66:1-19 which is incorporated herein by reference. Representative pharmaceutically acceptable amides of the invention include those derived from ammonia, primary C_{1-6} alkyl amines and secondary di (C_{1-6} alkyl) amines. Secondary amines include 5- or 6-membered heterocyclic or heteroaromatic ring moieties containing at least one nitrogen atom and optionally between 1 and 2 additional heteroatoms. Preferred amides are derived from ammonia, C_{1-3} alkyl primary amines, and di (C_{1-2} alkyl)amines. Representative pharmaceutically acceptable esters of the invention include C_{1-7} alkyl, C_{5-7} cycloalkyl, phenyl, and phenyl(C_{1-6})alkyl esters. Preferred esters include methyl esters.

The invention also includes disclosed compounds having one or more functional groups (e.g., hydroxyl, amino, or carboxyl) masked by a protecting group. Some of these masked or protected compounds are pharmaceutically

acceptable; others will be useful as intermediates. Synthetic intermediates and processes disclosed herein, and minor modifications thereof, are also within the scope of the invention.

HYDROXYL PROTECTING GROUPS

Hydroxyl protecting groups include: ethers, esters, and protection for 1,2- and 1,3-diols. The ether protecting groups include: methyl, substituted methyl ethers, substituted ethyl ethers, substituted benzyl ethers, silyl ethers and conversion of silyl ethers to other functional groups.

Substituted Methyl Ethers

Substituted methyl ethers include: methoxymethyl, methylthiomethyl, *t*-utylthiomethyl, (phenyldimethylsilyl) methoxymethyl, benzyloxymethyl, *p*-ethoxybenzyloxymethyl, (4-methoxyphenoxy) methyl, guaiacolmethyl, *t*-butoxymethyl, 4-pentenyloxymethyl, siloxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloroethoxymethyl, bis(2-chloro- ethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl, tetrahydropyranyl, 3-bromotetrahydro-pyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-methoxytetrahydrothio-pyranyl, 4-methoxytetrahydrothiopyranyl *S,S*-dioxido, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, and 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-ethanobenzofuran-2-yl.

Substituted Ethyl Ethers

Substituted ethyl ethers include: 1-ethoxyethyl, 1-(2,chloroethoxy)ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilyethyl, 2-(phenylselenyl)ethyl, *t*-butyl, allyl, *p*-chlorophenyl, *p*-methoxyphenyl, 2,4-dinitrophenyl, and benzyl.

Substituted Benzyl Ethers

Substituted benzyl ethers include: *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-halobenzyl, 2,6-dichlorobenzyl, *p*-cyanobenzyl, *p*-phenylbenzyl, 2- and 4-picolyl, 3-methyl-2-picolyl *N*-oxido, diphenylmethyl, *p*, *p'*-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl, α-naphthyldiphenyl-methyl, *p*-methoxyphenyldiphenylmethyl, di(*p*-methoxyphenyl)phenylmethyl,

tri-(*p*-methoxyphenyl)methyl, 4-(4′-bromophenacyloxy)phenyldiphenylmethyl, 4,4′,4″-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4′,4″-tris(levulinoyloxyphenyl) methyl, 4,4′,4″tris(benzoyloxyphenyl)methyl, 3-(imidazol-1-ylmethyl)bis(4′,4″-dimethoxyphenyl)-methyl, 1,1-bis(4-methoxyphenyl)-1′-pyrenylmethyl, 9-anthryl, 9-(9-phenyl) xanthenyl, 9-(9-phenyl-10-oxo) anthryl, 1,3-benzodithiolan-2-yl, and benzisothiazolyl *S,S*-dioxido.

Silyl Ethers

Silyl ethers include: trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylthexylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, and *t*-butylmethoxyphenylsilyl.

ESTERS

Esters protecting groups include: esters, carbonates, assisted cleavage, miscellaneous esters, and sulfonates.

Esters

Examples of protective esters include: formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, *p*-P-phenylacetate, 3-phenylpropionate, 4-oxopentanoate (levulinate), 4,4-(ethylenedithio) pentanoate, pivaloate, adamantoate,crotonate,4-methoxycrotonate, benzoate, *p*-phenylbenzoate, and 2,4,6-trimethylbenzoate (mesitoate).

Carbonates

Carbonates include: methyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloroethyl, 2-(trimethylsilyl) ethyl, 2-(phenylsulfonyl) ethyl, 2-(triphenylphosphonio) ethyl, isobutyl, vinyl, allyl, *p*-nitrophenyl, benzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, S-benzyl thiocarbonate, 4-ethoxy-1-naphthyl, and methyl dithiocarbonate.

Assisted Cleavage

Examples of assisted cleavage protecting groups include: 2-iodobenzoate, 4-azido-butyrate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl) benzoate, 2-formylbenzene-sulfonate, 2-(methylthiomethoxy) ethyl carbonate, 4-(methylthiomethoxymethyl) benzoate, and 2-(methylthiomethoxymethyl) benzoate.

Miscellaneous Esters

In addition to the above classes, miscellaneous esters include: 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl) phenoxyacetate, 2,4-bis(1,1-dimethylpropyl) phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)-2-methyl-2-butenoate (tigloate), *o*-(methoxycarbonyl) benzoate, *p*-P-benzoate, α-naphthoate, nitrate, alkyl *N,N,N' N'*-tetramethylphosphorodiamidate, *N*-phenylcarbamate, borate, dimethylphosphinothioyl, and 2,4-dinitrophenylsulfenate.

Sulfonates

Protective sulfates includes: sulfate, methanesulfonate(mesylate), benzylsulfonate, and tosylate.

PROTECTION FOR 1,2- AND 1,3-DIOLS

The protection for 1,2 and 1,3-diols group includes: cyclic acetals and ketals, cyclic ortho esters, and silyl derivatives.

Cyclic Acetals and Ketals

Cyclic acetals and ketals include: methylene, ethylidene, 1-*t*-butylethylidene, 1-phenylethylidene, (4-methoxyphenyl) ethylidene, 2,2,2-trichloroethylidene, acetonide (isopropylidene), cyclopentylidene, cyclohexylidene, cycloheptylidene, benzylidene, *p*-methoxybenzylidene, 2,4-dimethoxybenzylidene, 3,4-dimethoxybenzylidene, and 2-nitrobenzylidene.

Cyclic Ortho Esters

Cyclic ortho esters include: methoxymethylene, ethoxymethylene, dimethoxy-methylene, 1-methoxyethylidene, 1-ethoxyethylidine, 1,2-dimethoxyethylidene,

α-methoxybenzylidene, 1-(*N,N*-dimethylamino)ethylidene derivative, α-(*N,N*-dimethylamino) benzylidene derivative, and 2-oxacyclopentylidene.

PROTECTION FOR THE CARBOXYL GROUP

ESTERS

Ester protecting groups include: esters, substituted methyl esters, 2-substituted ethyl esters, substituted benzyl esters, silyl esters, activated esters, miscellaneous derivatives, and stannyl esters.

Substituted Methyl Esters

Substituted methyl esters include: 9-fluorenylmethyl, methoxymethyl, methylthiomethyl, tetrahydropyranyl, tetrahydrofuranyl, methoxyethoxymethyl, 2-(trimethylsilyl)ethoxy-methyl, benzyloxymethyl, phenacyl, *p*-bromophenacyl, α-methylphenacyl, *p*-methoxyphenacyl, carboxamidomethyl, and *N*-phthalimidomethyl.

2-Substituted Ethyl Esters

2-Substituted ethyl esters include: 2,2,2-trichloroethyl, 2-haloethyl, ω-chloroalkyl, 2-(trimethylsily)ethyl, 2-methylthioethyl, 1,3-dithianyl-2-methyl, 2(*p*-nitrophenylsulfenyl)-ethyl, 2-(*p*-toluenesulfonyl)ethyl, 2-(2′-pyridyl)ethyl, 2-(diphenylphosphino)ethyl, 1-methyl-1-phenylethyl, *t*-butyl, cyclopentyl, cyclohexyl, allyl, 3-buten-1-yl, 4-(trimethylsily)-2-buten-1-yl, cinnamyl, α-methylcinnamyl, phenyl, *p*-(methylmercapto)-phenyl, and benzyl.

Substituted Benzyl Esters

Substituted benzyl esters include: triphenylmethyl, diphenylmethyl, bis(*o*-nitrophenyl)methyl, 9-anthrylmethyl, 2-(9,10-dioxo)anthrylmethyl, 5-dibenzo-suberyl, 1-pyrenylmethyl,2-(trifluoromethyl)-6-chromylmethyl, 2,4,6-trimethylbenzyl, *p*-bromobenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-methoxybenzyl, 2,6-dimethoxybenzyl, 4-(methylsulfinyl)benzyl, 4-sulfobenzyl, piperonyl, and 4-P-benzyl.

Silyl Esters

Silyl esters include: trimethylsilyl, triethylsilyl, *t*-butyldimethylsilyl, *i*-propyldimethylsilyl, phenyldimethylsilyl, and di- *t*-butylmethylsilyl.

Miscellaneous Derivatives

Miscellaneous derivatives includes: oxazoles, 2-alkyl-1,3-oxazolines, 4-alkyl-5-oxo-1,3-oxazolidines, 5-alkyl-4-oxo-1,3-dioxolanes, ortho esters, phenyl group, and pentaaminocobalt(III) complex.

Stannyl Esters

Examples of stannyl esters include: triethylstannyl and tri-*n*-butylstannyl.

AMIDES AND HYDRAZIDES

Amides include: *N,N* –dimethyl, pyrrolidinyl, piperidinyl, 5,6-dihydrophenanthridinyl, *o*-nitroanilides, *N*-7-nitroindolyl, *N*-8-nitro-1,2,3,4-tetrahydroquinolyl, and *p*-P-benzenesulfonamides. Hydrazides include: *N*-phenyl, *N,N'*-diisopropyl and other dialkyl hydrazides.

PROTECTION FOR THE AMINO GROUP

CARBAMATES

Carbamates include: carbamates, substituted ethyl, assisted cleavage, photolytic cleavage, urea-type derivatives, and miscellaneous carbamates.

Carbamates

Carbamates include: methyl and ethyl, 9-fluorenylmethyl, 9-(2-sulfo)fluorenylmethyl, 9-(2,7-dibromo)fluorenylmethyl, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydro- thioxanthyl)]methyl, and 4-methoxyphenacyl.

Substituted Ethyl

Substituted ethyl protective groups include: 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1-(1-adamantyl)-1-methylethyl, 1,1-dimethyl-2-haloethyl, 1,1dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenylyl)ethyl, 1-(3,5-di-*t*-butylphenyl)-1-methylethyl, 2-(2'-and 4'-pyridyl)ethyl, 2-(*N,N*-icyclohexylcarboxamido)- ethyl, *t*-butyl, 1-adamantyl, vinyl, allyl, 1-isopropylallyl, connamyl, 4-nitrocinnamyl, quinolyl, *N*-hydroxypiperidinyl, alkyldithio, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, *p*-bromobenzyl, *p*-chlorobenzyl, 2,4dichlorobenzyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl, and diphenylmethyl.

Assisted Cleavage

Protection via assisted cleavage includes: 2-methylthioethyl, 2-methylsulfonylethyl, 2-(*p*-toluenesulfonyl)ethyl, [2-(1,3-dithianyl)]methyl, 4-methylthiophenyl, 2,4-dimethyl-thiophenyl, 2-phosphonioethyl, 2-triphenylphosphonioisopropyl, 1,1-dimethyl-2cyanoethyl, *m*-chloro-*p*-acyloxybenzyl, *p*-(dihydroxyboryl)benzyl, 5-benzisoxazolyl-methyl, and 2-(trifluoromethyl)-6-chromonylmethyl.

Photolytic Cleavage

Photolytic cleavage methods use groups such as: *m*-nitrophenyl, 3,5-dimethoxybenzyl, *o*-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, and phenyl(*o*-nitrophenyl)methyl.

Urea-Type Derivatives

Examples of of urea-type derivatives include: phenothiazinyl-(10)-carbonyl derivative, *N'*-p-toluenesulfonylaminocarbonyl, and *N'*-phenylaminothiocarbonyl.

Miscellaneous Carbamates

In addition to the above, miscellaneous carbamates include: *t*-amyl, *S*-benzyl thiocarbamate, *p*-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, *p*-decyloxy-benzyl, diisopropylmethyl, 2,2-dimethoxycarbonylvinyl, *o*-(*N,N*-dimethyl-carboxamido)-benzyl, 1,1-dimethyl-3(*N,N*-dimethylcarboxamido)propyl, 1,1-dimethyl-propynyl, di(2-pyridyl)methyl, 2-furanylmethyl, 2-iodoethyl, isobornyl, isobutyl, isonicotinyl, *p*(*p'*-methoxyphenyl- azo)benzyl, 1-methylcyclobutyl, 1-methylcyclohexyl, 1-methyl-1-cyclopropyl- methyl, 1-methyl-(3,5-dimethoxyphenyl)ethyl, 1-methyl-1(*p*-henylazophenyl)- ethyl, 1-methyl-1-phenylethyl, 1-methyl-1-(4-pyridyl)ethyl, phenyl, *p*-(phenylazo)benzyl, 2,4,6-tri-*t*-butylphenyl, 4-(trimethylammonium) benzyl, and 2,4,6-trimethylbenzyl.

AMIDES

Amides

Amides includes: *N*-formyl, *N*-acetyl, *N*-chloroacetyl, *N*-trichloroacetyl, *N*-trifluoroacetyl, *N*-phenylacetyl, *N*-3-phenylpropionyl, *N*-picolinoyl, *N*-3-pyridyl-carboxamide, *N*-benzoylphenylalanyl derivative, *N*-benzoyl, and *N*-*p*-phenylbenzoyl.

Assisted Cleavage

Assisted cleavage groups include: *N*-*o*-nitrophenylacetyl, *N*-*o*-nitrophenoxyacetyl, *N*-acetoacetyl, (*N*'-dithiobenzyloxycarbonylamino)acetyl, *N*-3-(*p*-hydroxphenyl) propionyl, *N*-3-(*o*-nitrophenyl)propionyl, *N*-2-methyl-2-(*o*-nitrophenoxy)propionyl, *N*-2-methyl-2-(*o*-phenylazophenoxy)propionyl, *N*-4-chlorobutyryl, *N*-3-methyl-3-nitrobutyryl, *N*-*o*-nitrocinnamoyl, *N*-acetylmethionine derivative, *N*-*o*-nitrobenzoyl, *N*-*o*-(benzoyloxymethyl)benzoyl, and 4,5-diphenyl-3-oxazolin-2-one.

Cyclic Imide Derivatives

Cyclic imide derivatives include: *N*-phthalimide, *N*-dithiasuccinoyl, *N*-2,3-diphenyl-maleoyl, *N*-2,5-dimethylpyrrolyl, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct, 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, and 1-substituted 3,5-dinitro-4-pyridonyl.

SPECIAL -NH PROTECTIVE GROUPS

Protective groups for – NH include: *N*-alkyl and *N*-aryl amines, imine derivatives, enamine derivatives, and *N*-hetero atom derivatives (such as *N*-metal, N-N, N-P, N-Si, and N-S), *N*-sulfenyl, and *N*-sulfonyl.

N-Alkyl and *N*-Aryl Amines

N-alkyl and *N*-aryl amines include: *N*-methyl, *N*-allyl, *N*-[2-(trimethylsilyl)ethoxyl]-methyl, *N*-3-acetoxypropyl, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), quaternary ammonium salts, *N*-benzyl, *N*-di(4-methoxyphenyl)methyl, *N*-5-dibenzosuberyl, *N*-triphenylmethyl, *N*-(4-methoxyphenyl)diphenylmethyl, *N*-9-phenylfluorenyl,

N-2,7-dichloro-9-fluorenylmethylene, *N*-ferrocenylmethyl, and *N*-2-picolylamine *N* '-oxide.

Imine Derivatives

Imine derivatives include: *N*-1,1-dimethylthiomethylene, *N*-benzylidene, *N*-*p*-methoxybenzylidene, *N*-diphenylmethylene, *N*-[(2-pyridyl)mesityl]methylene, *N*-(*N* ',*N* '-dimethylaminomethylene), *N*,*N* '-isopropylidene, *N*-*p*-nitrobenzylidene, *N*-salicylidene, *N*-5-chlorosalicylidene, *N*-(5-chloro-2-hydroxyphenyl)phenyl-methylene, and *N*-cyclohexylidene.

Enamine Derivative

An example of an enamine derivative is *N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl).

N-Hetero Atom Derivatives

N-metal derivatives include: *N*-borane derivatives, *N*-diphenylborinic acid derivative, *N*-[phenyl(pentacarbonylchromium- or -tungsten)]carbenyl, and *N*-copper or *N*-zinc chelate. Examples of *N*-*N* derivatives include: *N*-nitro, *N*-nitroso, and *N*-oxide. Examples of *N*-P derivatives include: *N*-diphenylphosphinyl, *N*-dimethylthiophosphinyl, *N*-diphenylthiophosphinyl, *N*-dialkyl phosphoryl, *N*-dibenzyl phosphoryl, and *N*-diphenyl phosphoryl. Examples of *N*-sulfenyl derivatives include: *N*-benzenesulfenyl, *N*-*o*-nitrobenzenesulfenyl, *N*-2,4-dinitrobenzenesulfenyl, *N*-pentachlorobenzenesulfenyl, *N*-2-nitro-4-methoxy-benzenesulfenyl, *N*-triphenylmethylsulfenyl, and *N*-3-nitropyridinesulfenyl. *N*-sulfonyl derivatives include: *N*-*p*-toluenesulfonyl, *N*-benzenesulfonyl, *N*-2,3,6-trimethyl-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethoxybenzenesulfonyl, *N*-2,6-dimethyl-4-methoxy-benzenesulfonyl, *N*-pentamethylbenzenesulfonyl, *N*-2,3,5,6-tetramethyl-4-methoxybenzene- sulfonyl, *N*-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethylbenzenesulfonyl, *N*-2,6-dimethoxy- 4-methylbenzenesulfonyl, *N*-2,2,5,7,8-pentamethylchroman-6-sulfonyl, *N*-methanesulfonyl,

N-β-trimethylsilylethanesulfonyl, *N*-9-anthracenesulfonyl, *N*-4-(4',8'-dimethoxynaphthylmethyl)-benzenesulfonyl, *N*-benzylsulfonyl, *N*-trifluoromethylsulfonyl, and *N*-phenacylsulfonyl.

Disclosed compounds which are masked or protected may be prodrugs, compounds metabolized or otherwise transformed *in vivo* to yield a disclosed compound, e.g., transiently during metabolism. This transformation may be a hydrolysis or oxidation which results from contact with a bodily fluid such as blood, or the action of acids, or liver, gastrointestinal, or other enzymes.

Features of the invention are further described in the examples below.

E. Examples

BIOLOGICAL EXAMPLES

Example 1

Effect of PD 198306 on streptozocin-induced static allodynia

Animals

Male Sprague Dawley rats (250-300g), obtained from Bantin and Kingman, (Hull, U.K.) were housed in groups of 3. All animals were kept under a 12h light/dark cycle (lights on at 07h 00min) with food and water *ad libitum.* All experiments were carried out by an observer blind to drug treatments.

Development of diabetes in the rat

Diabetes was induced in rats by a single i.p. injection of streptozocin (50 mg/kg) as described previously (Courteix et al., 1993).

Evaluation of static allodynia

Mechanical hypersensitivity was measured using Semmes-Weinstein von Frey hairs (Stoelting, Illinois, U.S.A.). Animals were placed into wire mesh bottom cages allowing access to the underside of their paws. Animals were habituated to this environment prior to the start of the experiment. Mechanical hypersensitivity was tested by touching the plantar surface of the animals right hind paw with von Frey hairs in ascending order of force (0.7, 1.2, 1.5, 2, 3.6, 5.5, 8.5, 11.8, 15.1 and 29g) for up to 6 sec. Once a withdrawal response was established, the paw was re-tested, starting with the next descending von Frey hair until no response occurred. The highest force of 29 g lifted the paw as well as eliciting a response, thus represented the cut off point. The lowest amount of force required to elicit a response was recorded as the paw withdrawal threshold (PWT) in grams.

Drugs

PD 198306 [N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide] and CI-1008 (pregabalin) were synthesized at Parke-Davis (Ann Arbor, MI, USA). PD 198306 was suspended in cremophor:ethanol:water (1:1:8) vehicle. Pregabalin was dissolved in water. Both compounds were administered orally. Streptozocin (Aldrich, UK) was dissolved in 0.9% w/v NaCl and administered intraperitoneally. Drug administrations were made in a volume of 1 ml/kg.

Statistics

The static allodynia data were analysed using a Kruskall-Wallis ANOVA for non-parametric results, followed when significant by Mann-Whitney's t test.

Experimental protocol

Static allodynia was assessed with von Frey hairs, before (baseline, BL) and 1h after oral administration of PD 198306 (30mg/kg, p.o.), vehicle (cremophor:ethanol:water, 1:1:8) or pregabalin (30mg/kg, p.o.) (test). Animals were administered again the same compounds on the following day, both in the morning and the afternoon. Static allodynia was assessed only before and 1h after the afternoon administration, in order to minimise the habituation of the animals to the testing conditions. Animals treated with pregabalin received water in the morning administration, in order to avoid the potential development of tolerance to the compound with repeated administration.

Day 1:	Day 2:
	a.m.: PD 198306
	Water
	Vehicle
p.m.: **BL**	p.m.: **BL**

PD 198306	PD 198306
Pregabalin	Pregabalin
Vehicle	Vehicle
Test	**Test**

RESULTS

A single administration of pregabalin (30mg/kg, p.o.) significantly blocked streptozocin-induced static allodynia 1h after administration. In contrast, a single administration of PD 198306 (30mg/kg, p.o) had no effect on streptozocin-induced static allodynia 1h after administration (see below). However, after the compound had been administered twice more on the following day, it significantly blocked streptozocin-induced static allodynia 1h after the third administration. The effects had disappeared by the following day (see FIG. 1).

Example 2

MATERIALS AND METHODS

Animals

Male Sprague Dawley rats (250-300g), obtained from Charles River, Margate, U.K.) were housed in groups of 3-6. All animals were kept under a 12h light/dark cycle (lights on at 07h 00min) with food and water *ad libitum*. All experiments were carried out by an observer blind to drug treatments.

Diabetes was induced in rats by a single i.p. injection of streptozocin (50mg/kg) as described previously (Courteix et al., 1993).

Development of Chronic Constriction Injury in the rat

Animals were anaesthetised with 2% isoflurane 1:4 O_2/N_20 mixture maintained during surgery via a nose cone. The sciatic nerve was ligated as previously described by Bennett and Xie, 1988. Animals were placed on a homeothermic blanket for the duration of the procedure. After surgical preparation the common sciatic nerve was exposed at the middle of the thigh

by blunt dissection through biceps femoris. Proximal to the sciatic trifurcation, about 7mm of nerve was freed of adhering tissue and 4 ligatures (4-0 silk) were tied loosely around it with about 1mm spacing. The incision was closed in layers and the wound treated with topical antibiotics.

Intrathecal injections

PD 198306 and pregabalin were administered intrathecally in a volume of 10 μl using a 100 μl Hamilton syringe by exposing the spine of the rats under brief isoflurane anaesthesia. Injections were made into the intrathecal space between lumbar region 5-6 with a 10 mm long 27 gauge needle. Penetrations were judged successful if there was a tail flick response. The wound was sealed with an autoclip and rats appeared fully awake within 2-3 min following injection.

Evaluation of static allodynia

Mechanical hypersensitivity was measured using Semmes-Weinstein von Frey hairs (Stoelting, Illinois, U.S.A.). Animals were placed into wire mesh bottom cages allowing access to the underside of their paws. Animals were habituated to this environment prior to the start of the experiment. Mechanical hypersensitivity was tested by touching the plantar surface of the animals right hind paw with von Frey hairs in ascending order of force (0.7, 1.2, 1.5, 2, 3.6, 5.5, 8.5, 11.8, 15.1 and 29g) for up to 6sec. Once a withdrawal response was established, the paw was re-tested, starting with the next descending von Frey hair until no response occurred. The highest force of 29g lifted the paw as well as eliciting a response, thus represented the cut off point. The lowest amount of force required to elicit a response was recorded as the paw withdrawal threshold (PWT) in grams.

Experimental protocol

Static allodynia was assessed with von Frey hairs, before (baseline, BL) and 0.5h, 1h and 2h after intrathecal or intraplantar administration of PD 198306 (1-30μg, i.t.), vehicle (cremophor:ethanol:water, 1:1:8) or pregabalin (10μg, i.t). For oral administration experiments, static allodynia was assessed

with von Frey hairs, before (baseline, BL) and 1h after oral administration of PD 198306 (3-30mg/kg, p.o.), vehicle (cremophor:ethanol:water, 1:1:8) or pregabalin (30mg/kg, p.o.). Animals were administered again the same compounds on the following day, both in the morning and the afternoon. Static allodynia was assessed before and 1h after the morning administration. In the afternoon static allodynia was assessed before, 1h, 2h and 3h after administration for streptozocin treated animals. CCI animals were assessed before, 1h and 2h after administration

Drugs used

PD 198306 and pregabalin were synthesised at Parke-Davis (Ann Arbor, MI, USA). PD 198306 was suspended in cremophor:ethanol:water (1:1:8) vehicle. Pregabalin was dissolved in water. Both compounds were administered orally, intrathecally or intraplantar in volumes of 1ml/kg, 10µl and 100µl respectively. Streptozocin (Aldrich, UK) was dissolved in 0.9% w/v NaCl and administered intraperitoneally in a volume of 1ml/kg.

Statistics

Data were analysed using a Kruskall-Wallis ANOVA for non-parametric results, followed when significant by Mann-Whitney's t test *vs* vehicle group.

RESULTS

1. Effects of PD 198306 on static allodynia, following systemic administration

1.1. Effect of PD198306 on streptozocin-induced static allodynia

A single administration of pregabalin (30mg/kg, p.o.) significantly blocked streptozocin-induced static allodynia 1h after administration. In contrast, a single administration of PD 198306 (3-30mg/kg, p.o) had no effect on streptozocin-induced static allodynia 1h after administration (FIG. 2). However, after the compound had been administered twice more on the following day, PD 198306 (30mg/kg) significantly blocked streptozocin-induced static allodynia for 2h after the third administration (FIG. 2).

1.2. Effect of PD198306 on CCI-induced static allodynia

A single administration of pregabalin (30mg/kg, p.o.) significantly blocked CCI-induced static allodynia 1h after administration. In contrast, neither a single or multiple administration of PD 198306 (3-30mg/kg, p.o) had any effect on CCI-induced static allodynia (FIG. 3).

2. Effects of PD 198306 on static allodynia, following intrathecal administration

Intrathecally administered PD198306 (1-30μg) dose-dependently blocked the maintenance of static allodynia in both streptozocin (FIG. 4) and CCI animals (FIG. 5) with respective MEDs of 3 and 10 μg. This antiallodynic effect lasted for 1h.

3. Effects of PD 198306 on static allodynia, following intraplantar administration

An intrathecal administration of PD 198306 (30μg) significantly blocked static allodynia in both neuropathic pain models (FIGS. 6,7). In contrast, a single administration of PD 198306 at a dose 100-fold higher (3mg/100μl) directly into the paw had no effect on streptozocin (FIG. 6) or CCI-induced static allodynia (FIG. 7).

REFERENCES

Bennett GJ, Xie Y-K. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. Pain 1988;33:87-107.

Courteix C, Eschalier A and Lavarenne J. Streptozocin –induced rats: behavioural evidence for a model of chronic pain. Pain 1993;53:81-8

Example 3

Effect of other MEK inhibitors in a neuropathic pain model in the rat

SUMMARY

The effect of several MEK inhibitors, with different binding affinities, has been investigated in the CCI model of neuropathic pain in the rat, by assessing static allodynia with von Frey hairs. Intrathecal administration of PD219622 or PD297447 (30μg) had no significant effect on allodynia. This lack of effect may reflect the low affinity or solubility of the compounds. However, intrathecal administration of PD 254552 or PD 184352 (30μg), which posses higher binding affinities, blocked the maintenance of static allodynia in CCI animals. The antiallodynic effect was only evident for 30min post-injection and thus, shorter than the one observed for pregabalin (100μg). The magnitude of the effect was similar for 30μg of PD 184352 and 100μg of pregabalin. From this study it is concluded that MEK inhibitors exert an antiallodynic effect in CCI-induced neuropathic rats when administered intrathecally, and that the antiallodynic effect correlates with the affinity of the compounds.

The animals and methods for developing chronic constriction injury in the rat, injecting test compounds, and evaluation of static allodynia were according to Example 2 above. PD219622, PD297447, PD 184352, PD 254552 and pregabalin were administered intrathecally at doses of 30μg for all PD compounds and 100μg for pregabalin. Static allodynia was assessed with von Frey hairs, before (baseline, BL) and 0.5h, 1h and 2h after intrathecal administration of the compounds

Drugs used

PD297447, PD219622, PD 254552, PD 184352 (CI-1040), and pregabalin were synthesised at Parke-Davis (Ann Arbor, MI, USA). PD297447, PD219622, PD 254552 and PD 184352 were suspended in

cremophor:ethanol:water (1:1:8) vehicle. Pregabalin was dissolved in water. All compounds were administered intrathecally in a 10μl volume.

Statistics

Data were analysed using a Kruskall-Wallis ANOVA for non-parametric results, followed when significant by Mann-Whitney's t test *vs* vehicle group.

RESULTS

Intrathecally administered PD297447 or PD219622 (30μg) had no significant effect on allodynia. This lack of effect may reflect the low affinity of the compounds (965nM and 100nM respectively). However, intrathecal administration of PD 184352 or PD 254552 (30μg) blocked the maintenance of static allodynia in CCI animals (see FIG. 8). These compounds possess higher affinity (2 and 5 nM respectively). The antiallodynic effect was only evident for 30min post-injection and thus, shorter than the one observed for pregabalin (100μg). The magnitude of the effect was similar for 30μg of PD 184352 and 100μg of pregabalin.

The results indicate that MEK inhibitors exert an antiallodynic effect in CCI-induced neuropathic rats when administered intrathecally, and that the antiallodynic effect correlates with the affinity of the compounds.

CHEMICAL EXAMPLES

EXAMPLE 1

[4-Chloro-2-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine (18). (Scheme 2, R_1=Cl, R_2=R_3=H, R_4=CH_3)

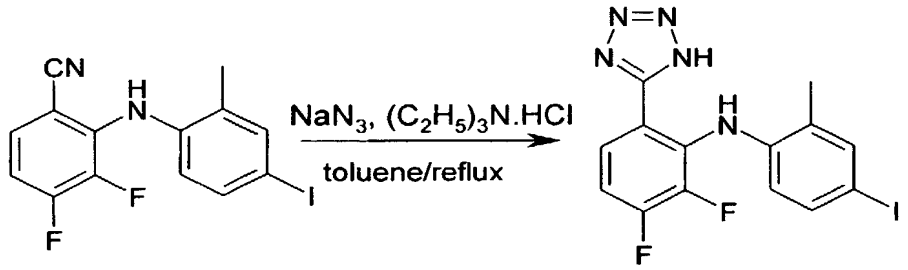
a). A mixture of 5-chloro-2-methoxybenzoic acid 16 (14.8 g, 0.0793 mole) and $SOCl_2$ (28.31 g, 14.97 ml, 0.1584 mole) was refluxed for 2 hours and excess $SOCl_2$ removed leaving a white residue. The solid was dissolved in CH_2Cl_2 and added to a solution of 2-amino-2-methyl-1-propanol (13.98 g, 14.97 ml, 0.1584 mole) in CH_2Cl_2 cooled with ice-bath. The ice-bath was removed, and after stirring at room temperature for 3 hours a white solid precipitated. The precipitate was separated by filtration and discarded. The filtrate was concentrated leaving a thick colorless oil. $SOCl_2$ (17.4 ml) was added to the oil dropwise. An exothermic reaction took place resulting in to a freely flowing solution. After stirring for 30 minutes, the reaction mixture was poured in to Et_2O (200 ml). An oil separated out. The Et_2O layer was removed by decanting and discarded. The oily residue was dissolved in a minimum amount of water, basified with aqueous 20% NaOH, and extracted with Et_2O. The Et_2O layer was dried (K_2CO_3) and concentrated to give **17** as tan oil. Yield 14.63 g (77%).

b). LDA (5 ml of 2.0 M solution in THF) was added to a solution of 4-iodo-2-methylaniline (2.33 g, 0.010 mole) in THF (15 ml) at –78 °C. The mixture was stirred at –78 °C for 30 minutes. To this, a solution of **17** (1.199 g, 0.005 mole) in THF (15 ml) was added. The mixture stirred for 16 hours as it warmed up to room temperature. The reaction mixture was quenched with aqueous NH_4Cl and extracted with Et_2O. The Et_2O layer was dried ($MgSO_4$) and concentrated to give crude **18** as brown oil. The oil was purified on silica column chromatography. Eluting with CH_2Cl_2 gave pure 1.7 g (77%) of **18** as brown oil. Four hundred and nine milligrams of the oil were dissolved in Et_2O and treated with Et_2O-HCl giving the HCl salt as a light yellow solid

precipitate. Yield 356.4 mg (81%); mp 324-330 °C; Anal. Calcd/found for $C_{18}H_{18}N_2OClI \bullet HCl.0.5H_2O$: C, 44.47/44.32; H, 4.15/3.94; N, 5.76/5.66.

EXAMPLE 2

[2,3-Difluoro-6-(1*H*-tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine



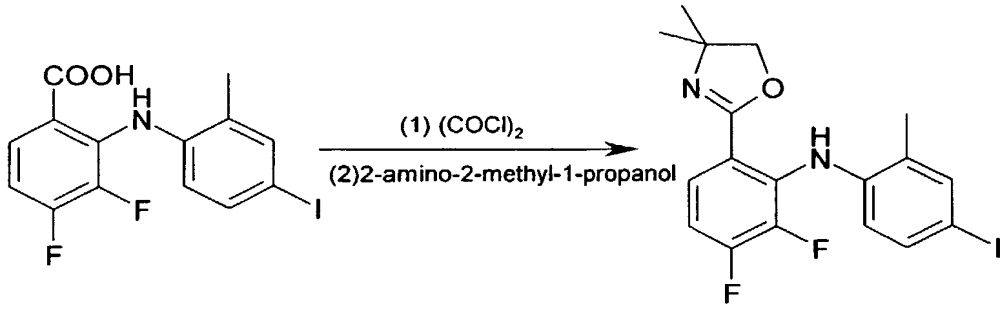
[2,3-Difluoro-6-cyano-phenyl]-(4-iodo-2-methyl-phenyl)-amine (1.11g, 3mmol) and Sodium azide(0.255g, 3.9mmol) and triethylamine hydrochloride (0.537g, 3.9mmol) were all suspended in 10ml toluene and stirred at 100°C for 12 hours. The mixture was concentrated and the residue purified by column chromatography with ethyl acetate/methanol (10/1) to give the product as a foam-like solid. The yield: ~50%

m.p: 83.4-88.7°C

^{1}H NMR($CDCl_3$, 400Hz): δ/ppm 7.69(1H, m, Phenyl-H); 7.42(1H, s, Phenyl-H); 7.27(1H, m, Phenyl-H); 6.91(1H, dd, J=16.2Hz, 8.3Hz, Phenyl-H); 6.40(1H, dd, Phenyl-H); 2.28(3H, s, CH_3)

EXAMPLE 3

[6-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-2,3-difluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine



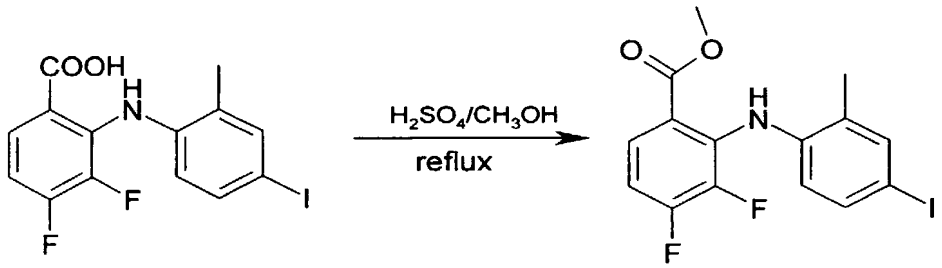
A solution of 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (1.17g, 3mmol), oxalyl chloride (0.457g, 3.6mmol) in 30ml dichloromethane was treated with 2 drops of dimethylformamide, stirred at room temperature for 3 hours then concentrated. The residue was dissolved in 25 ml dichloromethane then the solution was added dropwise to a solution of 2 amino-2-methyl-1-propanol (0.623g, 7mmol) in 25 ml dichloromethane at 0°C, then stirred at room temperature for 12 hours, filtered off the precipitate, the filtration was washed with water, 5% aqueous sodium bicarbonate, 1 N HCl, brine, dried with sodium sulfate. Concentration gave the crude product, then resuspended in 25 ml chloroform, then thionyl chloride was added at 0°C and stirred at room temperature for 15 hours, then concentrated and the residue was dissolved in 30 ml dichloromethane , 1 N HCl was added to adjusted the pH value to 11, the separated and extracted with chloroform, dried with sodium sulfate. Concentrated and then run column with hexanes/dichloromethane (20/1) to give the compound as a white crystal. The yield: 65%

m.p.: 103.7-104.4°C

^{1}H NMR($CDCl_3$, 400Hz): δ/ppm 10.2(1H, s, NH), 7.48-7.58(1H, m, Phenyl-H); 7.48(1H, s, Phenyl-H); 7.38(1H, d, J=8.5Hz, Phenyl-H), 6.66-6.72(1H, m, Phenyl-H); 6.58(1H, t, J=8.0Hz, Phenyl-H); 4.01(2H, s, -CH_2-); 2.31(3H, s, Phenyl-CH_3); 1.32(6H, s, -$C(CH_3)_2$-)

EXAMPLE 4

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid methyl ester



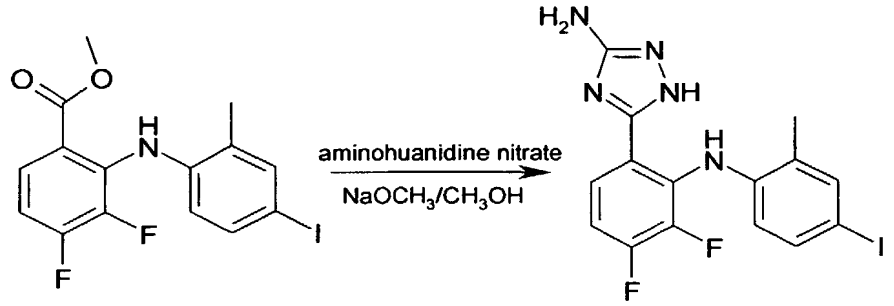
3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (5g) was dissolved in 100ml methanol and 5 drops of concentrated sulfuric acid was added, reflux for 4 days. Run column with hexanes/dichloromethane to give the product as a white solid, yield: 50%.

m.p.:90.1-90.4°C

^{1}H NMR($CDCl_3$, 400Hz): δ/ppm 8.92(1H, s, NH), 7.75-7.78(1H, m, Phenyl-H); 7.49(1H, s, Phenyl-H); 7.38(1H, dd, J=8.5Hz, 2.0Hz, Phenyl-H), 6.66-6.73(1H, m, Phenyl-H); 6.56-6.60(1H, m, Phenyl-H); 3.88(3H, s, -OCH_3); 2.30(3H, s, Phenyl-CH_3)

EXAMPLE 5

5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4*H*-[1,2,4]triazol-3-ylamine



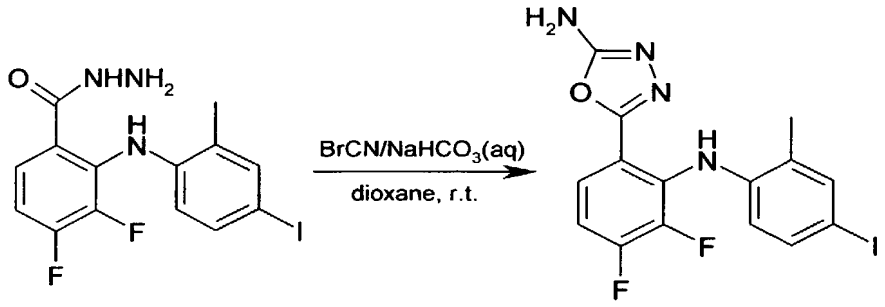
Aminoguanidine nitrate (1.65g, 12mmol) was added to a solution of sodium methoxide (0.648g, 12mmol) in methanol (12ml) at 0°C, then 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid methyl ester was added as a solution of methanol and refulx for 20 hours, concentration and run column with hexanes/ethyl acetate to give the product as a white crystal. The yield: 60%

m.p.: 191.7-192.0°C

^{1}H NMR(DMSO, 400Hz): δ/ppm 9.45(1H, s, -NH-); 7.79(1H, t, J=7.3Hz, Phenyl-H); 7.51(1H, s, Phenyl-H); 7.35(1H, d, J=10.1Hz, Phenyl-H); 7.05-7.11(1H, m, Phenyl-H); 6.44-6.48(1H, m, Phenyl-H); 6.32(2H, s, $-NH_2$), 2.32(3H, s, CH_3)

EXAMPLE 6

5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine

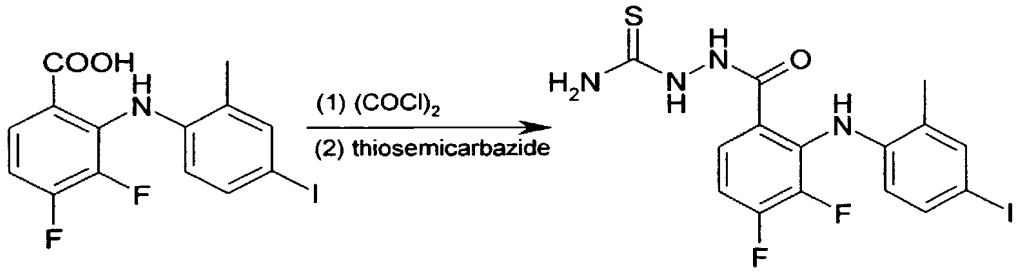


To a solution of 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid hydrazide (0.806g, 2mmol) in 5ml of dioxane was added cyanogen bromide (0.212g, 2mmol) followed by a solution of sodium bicarbonate (0.17g, 2mmol) in 5ml of water. The resulting mixture was stirred 18 hours at room temperature the solution was concentrated and the residure was run column with hexanes/ethyl acetate (3/1) to give the product which was recrystallized from ethyl acetate / hexanes to provide a pale-yellow crystal. The yield: 58%
m.p.: 183.7-184.0°C

^{1}H NMR($CDCl_3$, 400Hz): δ/ppm 8.87(1H, s, -NH-); 7.52(1H, s, Phenyl-H); 7.45-7.49(1H, m, Phenyl-H); 7.40(1H, d, J=8.3Hz, Phenyl-H); 6.77-6.83(1H, m, Phenyl-H); 6.60-6.63(1H, m, Phenyl-H); 5.02(2H, s, $-NH_2$), 2.36(3H, s, CH_3)

EXAMPLE 7

2-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoyl]hydrazinecarbothioamide



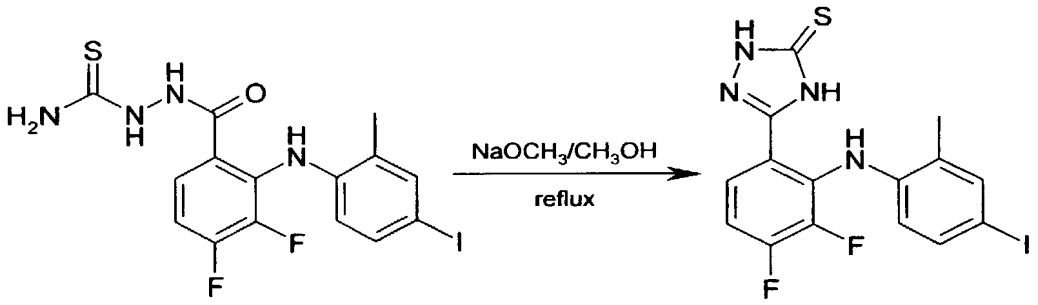
A solution of 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (3.9g, 0.01mol), oxalyl chloride (1.90g, 0.015mol) in 40ml dichloromethane was treated with 2 drops of dimethylformamide, stirred at room temperature for 3 hours before concentration. The residue was dissolved in 10 ml tetrahydrofuran and added to a solution of thiosemicarbazide (2.0g, 0.022mol) in 50ml tetrahydrofuran at 0°C, stirred at room temperature for 14 hours. Concentrated and run column chromatography with hexanes/ethyl acetate (1/1) to give the product as a yellow solid. 2.91g. The yield: 63%

m.p.: 159.5-160.0°C

^{1}H NMR(DMSO, 400Hz): δ/ppm 10.58(1H, s, -NH-); 9.28(1H, s, -NH-); 8.83(1H, s, -NH-); 7.95(1H, s, Phenyl-H); 7.12-7.75(2H, m, NH_2); 7.51(1H, s, Phenyl-H); 7.37(1H, dd, J=8.6Hz, 1.7Hz, Phenyl-H); 7.16(1H,dd, J=17Hz, 9.0Hz, Phenyl-H); 6.40-6.50(1H, m, Phenyl-H); 5.02(2H, s, -NH_2), 2.00(3H, s, CH_3)

EXAMPLE 8

5-[3,4-Difuoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4*H*-[1,2,4]triazole-3-thiol



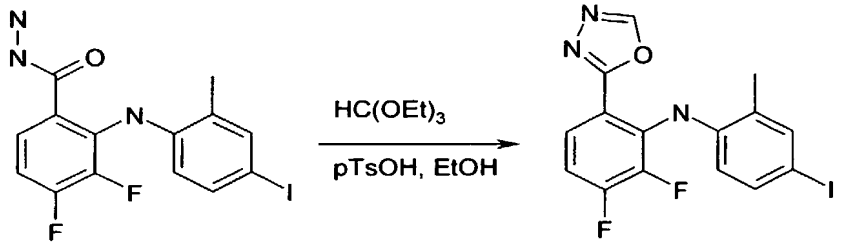
2-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoyl]hydrazinecarbothioamide (1.386g, 3mmol) was dissolved in 15 ml anhydrous methanol, sodium methoxide (25% wt% in methanol) 2.5ml was added at 0°C in one portion. The resulting mixture was heated at reflux for 17 hours before concentration. Run column with hexanes/ethyl acetate to give the product as a needle white crystal. The yield: 40%

m.p.: 196.5(dec.)

^{1}H NMR(DMSO, 400Hz): δ/ppm 13.87(1H, s, -NH-); 13.80(1H, s, -NH-); 8.16(1H, s, -NH-); 7.61-7.65(1H, m, Phenyl-H); 7.48(1H, s, Phenyl-H); 7.32(1H, dd, J=8.6Hz, 2.2Hz, Phenyl-H); 7.24(1H,dd, J=16.4Hz, 9.5Hz, Phenyl-H); 6.42-6.46(1H, m, Phenyl-H); 5.02(2H, s, $-NH_2$), 2.20(3H, s, CH_3).

EXAMPLE 9

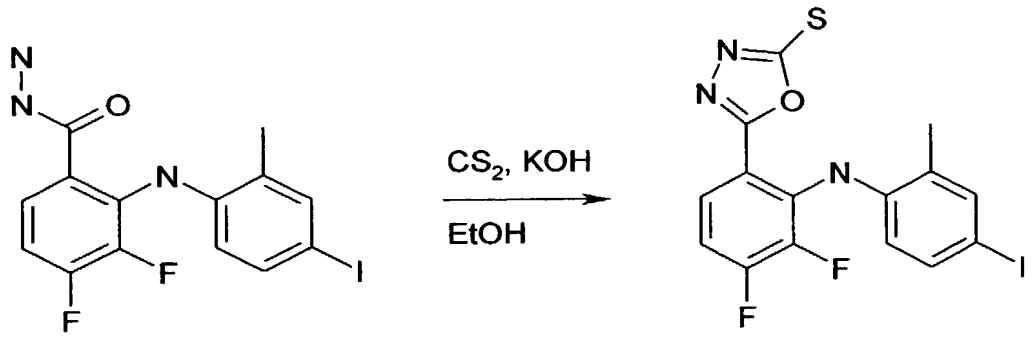
(2,3-Difluoro-6-[1,3,4]oxadiazol-2-yl-phenyl)-(4-iodo-2-methyl-phenyl)-amine



3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid hydrazide (146 mg, 0.36 mmol) was suspended in 7 mL of absolute EtOH and 2 mL of $HC(OEt)_3$ was added along with approximately 3 mg of pTsOH> The reaction was heated to reflux for 3h, cooled and concentration on a rotary evaporator. The reaction was purified (SiO2, 4:1 Hexane/EtOAc) to afford 117 mg (79%) of (2,3-difluoro-6-[1,3,4]oxadiazol-2-yl-phenyl)-(4-iodo-2-methyl-phenyl)-amine as a yellow powder. M.p. = 144.4 – 145.5 °C. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.44 (s, 1H), 7.66 (m, 1H), 7.52 (d, J = 1.7 Hz, 1 H), 7.38 (dd, J = 8.5, 1.9 Hz, 1 H), 6.83 (m, 1H), 6.14 (dd, J = 8.5, 5.9 Hz, 1 H), 2.37 (s, 3 H).

EXAMPLE 10

5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol



3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid hydrazide (170 mg, 0.42 mmol) was suspended in 7 mL of absolute EtOH and cooled to

0 °C. Carbon disulfide (74 mg, 0.97 mmol) was added followed by 24 mg (0.42 mmol) of powdered KOH. The reaction was stirred for 1 h at 0 °C, 1h at rt, and refluxed for 3 h to afford a homogeneous reaction. The reaction was cooled to rt, at which point a ppt formed. Water was added and the reaction diluted with 5 mL of EtOAc. 1N HCl was added to acidify the aqueous layer (pH = 2). The aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4 and concentrated to obtain 96 mg (51%) of 5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol as a yellow powder. M.p. = 231.8 – 232.8 °C. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.62 (m, 2H), 7.47 (s, 1H), 7.30 (complex m, 2H), 6.44 (dd, J = 8.0, 4.5 Hz, 1H), 2.19 (s, 3H).

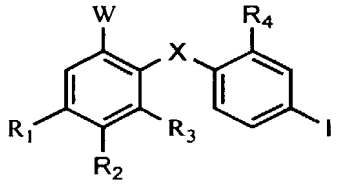
F. OTHER EMBODIMENTS

From the above disclosure and examples, and from the claims below, the essential features of the invention are readily apparent. The scope of the invention also encompasses various modifications and adaptations within the knowledge of a person of ordinary skill. Examples include a disclosed compound modified by addition or removal of a protecting group, or an ester, pharmaceutical salt, hydrate, acid, or amide of a disclosed compound. Publications cited herein are hereby incorporated by reference in their entirety.

What is claimed is:

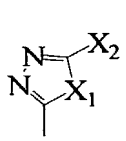
CLAIMS

1. A method for treating chronic pain, said method comprising administering to a subject in need of such treatment a composition comprising a MEK inhibitor selected from: a compound of formula (I):

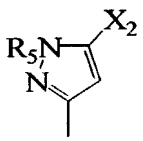


(I)

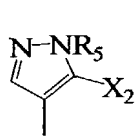
W is one of the following formulae (i) – (xiii):



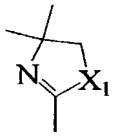
(i)



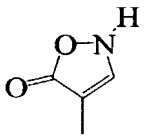
(ii)



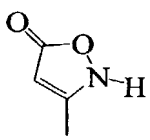
(iii)



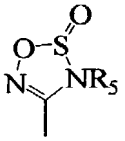
(iV)



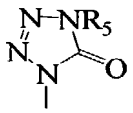
(v)



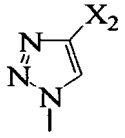
(vi)



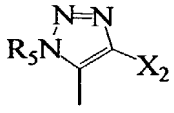
(vii)



(viii)



(ix)



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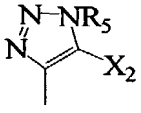
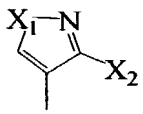


(xi)



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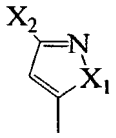
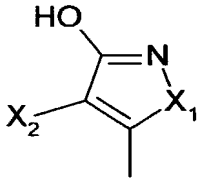
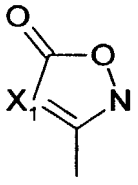


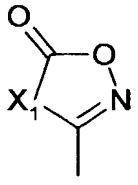
(xiii)



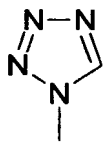
(xiv)



(xv)



(xvi)



(xvii)

X_1 is O, S, or NR_F;

X_2 is OH, SH, or NHR_E;

each of R_E and R_F is H or C $_{1-4}$ alkyl;

each of R_1 and R_2 is independently selected from H, F, NO_2, Br and Cl; R_1 can also be $SO_2NR_GR_H$, or R_1 and R_2 together with the benzene ring to which they are attached constitute an indole, isoindole, benzofuran, benzothiophene, indazole, benzimidazole, or benzthioazole;

R_3 is H or F;

each of R_G, R_H, and R_4 is independently selected from H, Cl and CH_3;

R_5 is H or C $_{3-4}$ alkyl; and

wherein each hydrocarbon radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, hydroxyl, amino, (amino)sulfonyl, and NO_2; and

wherein each heterocyclic radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, C $_{3-4}$ alkyl, C $_{3-6}$ cycloalkyl, C $_{3-4}$ alkenyl, C $_{3-4}$ alkynyl, phenyl, hydroxyl, amino, (amino)sulfonyl, and NO_2, wherein each substituent alkyl, cycloalkyl, alkenyl, alkynyl or phenyl is in turn optionally substituted with between 1 and 2 substituents independently selected from halo, C $_{1-2}$ alkyl, hydroxyl, amino, and NO_2;

or a pharmaceutically acceptable salt or C $_{1-8}$ ester thereof.

2. The method of claim 1, wherein said chronic pain is selected from neuropathic pain, idiopathic pain, and pain associated with chronic alcoholism, vitamin deficiency, uremia, or hypothyroidism.

3. The method of claim 2, wherein said chronic pain is a type of neuropathic pain.

4. The method of claim 3, wherein said neuropathic pain is associated with one of the following: inflammation, postoperative pain, phantom limb pain, burn pain, gout, trigeminal neuralgia, acute herpetic and postherpetic pain, causalgia, diabetic neuropathy, plexus avulsion, neuroma, vasculitis, viral infection, crush injury, constriction injury, tissue injury, limb amputation, post-operative pain, arthritis pain, and any other nerve injury between the peripheral nervous system and the central nervous system, inclusively.

5. The method of claim 2, wherein said chronic pain is associated with chronic alcoholism, vitamin deficiency, uremia, or hypothyroidism.

6. The method of claim 2, wherein said chronic pain is associated with idiopathic pain.

7. The method of claim 1, wherein said chronic pain is associated with inflammation.

8. The method of claim 1, wherein said chronic pain is associated with arthritis.

9. The method of claim 1, wherein said chronic pain is associated with post-operative pain.

10. The method of claim 1, wherein R_1 is bromo or chloro.

11. A method of claim 1, wherein R_2 is fluoro.

12. A method of claim 1, wherein R_3 is H.

13. A method of claim 12, wherein each of R_2 and R_3 is H.

14. A method of claim 1, wherein each of R_2 and R_3 is fluoro.

15. A method of claim 14, wherein R_1 is bromo.

16. A method of claim 14, wherein R_1 is fluoro.

17. A method of claim 1, wherein R_2 is nitro.

18. A method of claim 16, wherein R_3 is H.

19. A method of claim 1, wherein R_4 is chloro.

20. A method of claim 1, wherein R_4 is methyl.

21. A method of claim 1, wherein R_5 is H.

22. A method of claim 1, wherein R_5 is CH_3.

23. A method of claim 1, wherein X_1 is O or S.

24. A method of claim 1, wherein X_1 is NH or NCH_3.

25. A method of claim 1, wherein X_2 is OH, SH, or NH_2.

26. A method of claim 1, wherein X_2 is $NHCH_3$ or OH.

27. A method of claim 1, wherein said MEK inhibitor has a structure selected from: [5-fluoro-2-(1H-tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [2,3-difluoro-6-(1H-tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; (4-iodo-2-methyl-phenyl)-[2,3,4-trifluoro-6-(1H-tetrazol-5-yl)-phenyl]-amine; [4-bromo-2,3-difluoro-6-(1H-tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [5-fluoro-4-nitro-2-(1H-tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [2-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-5-fluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [6-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-2,3-difluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [6-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-2,3,4-trifluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [4-bromo-6-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-2,3-difluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [2-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-5-fluoro-4-nitro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; and 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-[1,2,4]triazol-3-ol.

28. A method of claim 1, wherein said MEK inhibitor has a structure selected from: 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; 5-[3,4,5-

trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; and 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-[1,2,4]triazole-3-thiol.

29. A method of claim 1, wherein said MEK inhibitor has a structure selected from: 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isothiazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isoxazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-1H-pyrazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isothiazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isoxazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-

methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol; 1-methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol; and 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-1-methyl-1H-pyrazol-3-ol.

30. A method of claim 1, wherein said MEK inhibitor has a structure selected from: 5-[2-(2-amino-4-iodo-phenylamino)-4-fluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-3,4-difluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-3,4,5-trifluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-5-bromo-3,4-difluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-4-fluoro-5-nitro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 3-methyl-5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3H-[1,2,3]triazol-4-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2-methyl-2H-pyrazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2-methyl-2H-pyrazol-3-ol; 2-methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-pyrazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2-methyl-2H-pyrazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-2-methyl-2H-pyrazol-3-ol; 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1,4-dihydro-tetrazol-5-one; 1-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-

1H-[1,2,3]triazol-4-ol; 1-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-[1,2,3]triazol-4-ol; 1-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-[1,2,3]triazol-4-ol; 1-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-[1,2,3]triazol-4-ol; and 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-1H-[1,2,3]triazol-4-ol.

31. The method of claim 1, wherein said MEK inhibitor has a structure selected from: 3-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-2H-isoxazol-5-one; [5-fluoro-2-(2-oxo-2,3-dihydro-2l>4_-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [2,3-difluoro-6-(2-oxo-2,3-dihydro-2l>4_-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; (4-Iodo-2-methyl-phenyl)-[2,3,4-trifluoro-6-(2-oxo-2,3-dihydro-2l>4_-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-amine; [4-bromo-2,3-difluoro-6-(2-oxo-2,3-dihydro-2l>4_-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [5-fluoro-4-nitro-2-(2-oxo-2,3-dihydro-2l>4_-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; 4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; and 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-isoxazol-5-one.

32. The method of claim 1, wherein said MEK inhibitor has a structure selected from: 2,4-bis-(2-chloro-4-iodo-phenylamino)-3fluoro5-nitro-benzoic acid; 5-[3,4difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; (2,3-difluoro-6-[1,3,4]oxadiazol-2-yl-phenyl)(-(4-iodo-2-

methyl-phenyl)-amine; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[3,4difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4*H*-[1,2,4]triazole-3-ylamine; and 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4*H*-[1,2,4]triazole-3-thiol.

33. The method of claim 1, wherein said MEK inhibitor has the structure: 2,4-bis-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-benzoic acid.

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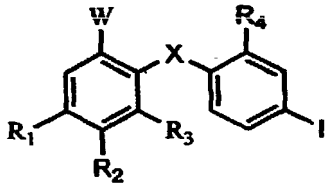
(54) Title: METHOD FOR TREATING CHRONIC PAIN USING MEK INHIBITORS



(I)

(57) Abstract: The invention features a method for treating chronic pain using the diarylamines disclosed in formula (I) of claim 1.

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FIG. 1

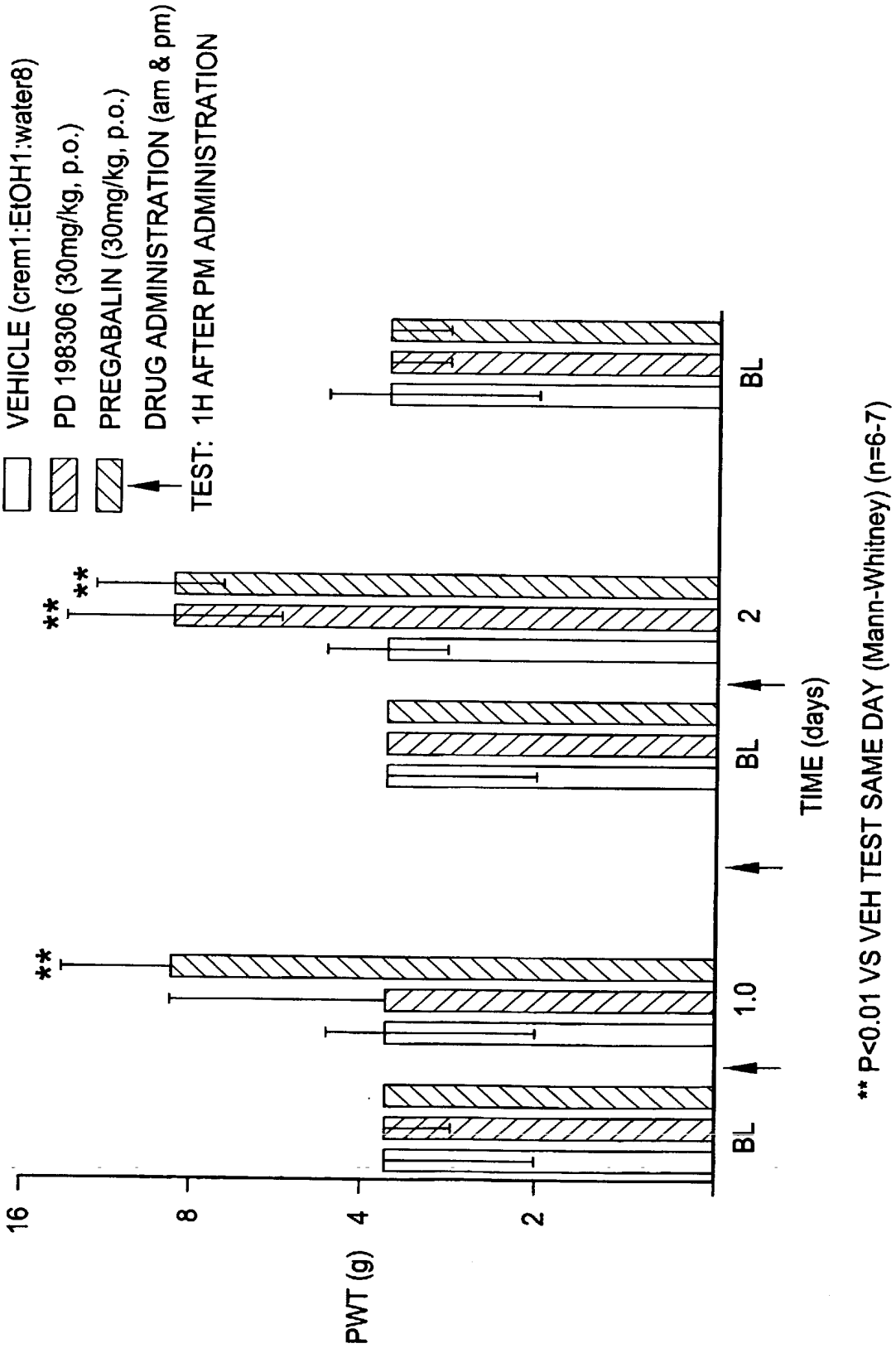
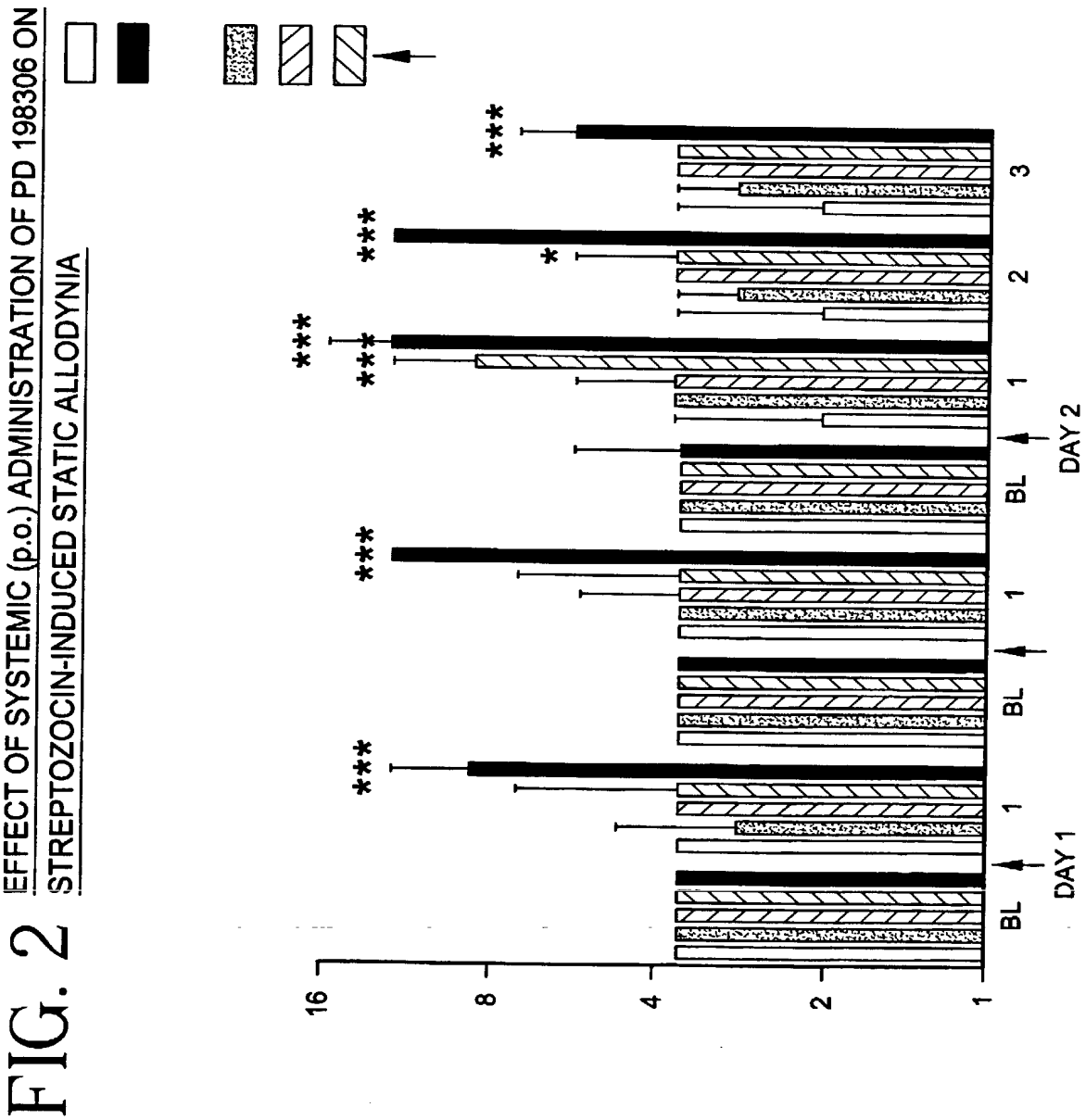

EFFECT OF PD 198306 ON STREPTOZOCIN-INDUCED STATIC ALLODYNIA
VEHICLE (crem1:EtOH1:water8)
PD 198306 (30mg/kg, p.o.)
PREGABALIN (30mg/kg, p.o.)
DRUG ADMINISTRATION (am & pm)
TEST: 1H AFTER PM ADMINISTRATION
PWT (g)
16
8
4
2
**
**
**
BL
1.0
BL
2
BL
TIME (days)
** P<0.01 VS VEH TEST SAME DAY (Mann-Whitney) (n=6-7)

FIG. 2


EFFECT OF SYSTEMIC (p.o.) ADMINISTRATION OF PD 198306 ON
STREPTOZOCIN-INDUCED STATIC ALLODYNIA
VEHICLE, P.O.
PREGABALIN, 30mg/kg, P.O.
PD 198306, mg/kg, P.O.
3
10
30
DRUG TREATMENT, P.O.
16
8
4
2
1
BL
1
BL
1
BL
1
2
3
DAY 1
DAY 2
***
***
***
***
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*

FIG. 3 EFFECT OF SYSTEMIC (p.o.) ADMINISTRATION OF PD 198306 ON CCI-INDUCED STATIC ALLODYNIA

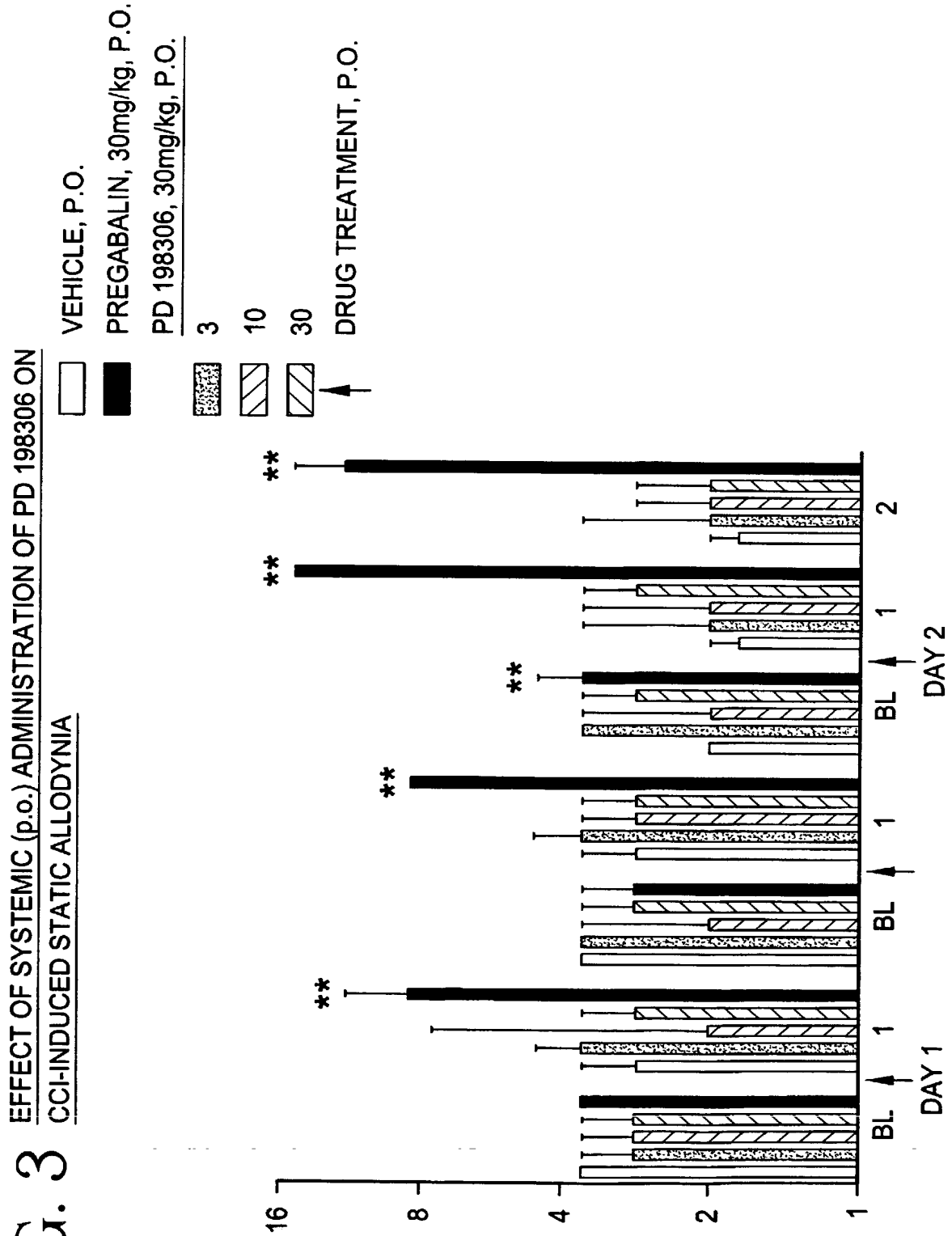


FIG. 4 EFFECT OF INTRATHECAL (i.t.) ADMINISTRATION OF PD 198306 ON STREPTOZOCIN-INDUCED STATIC ALLODYNIA

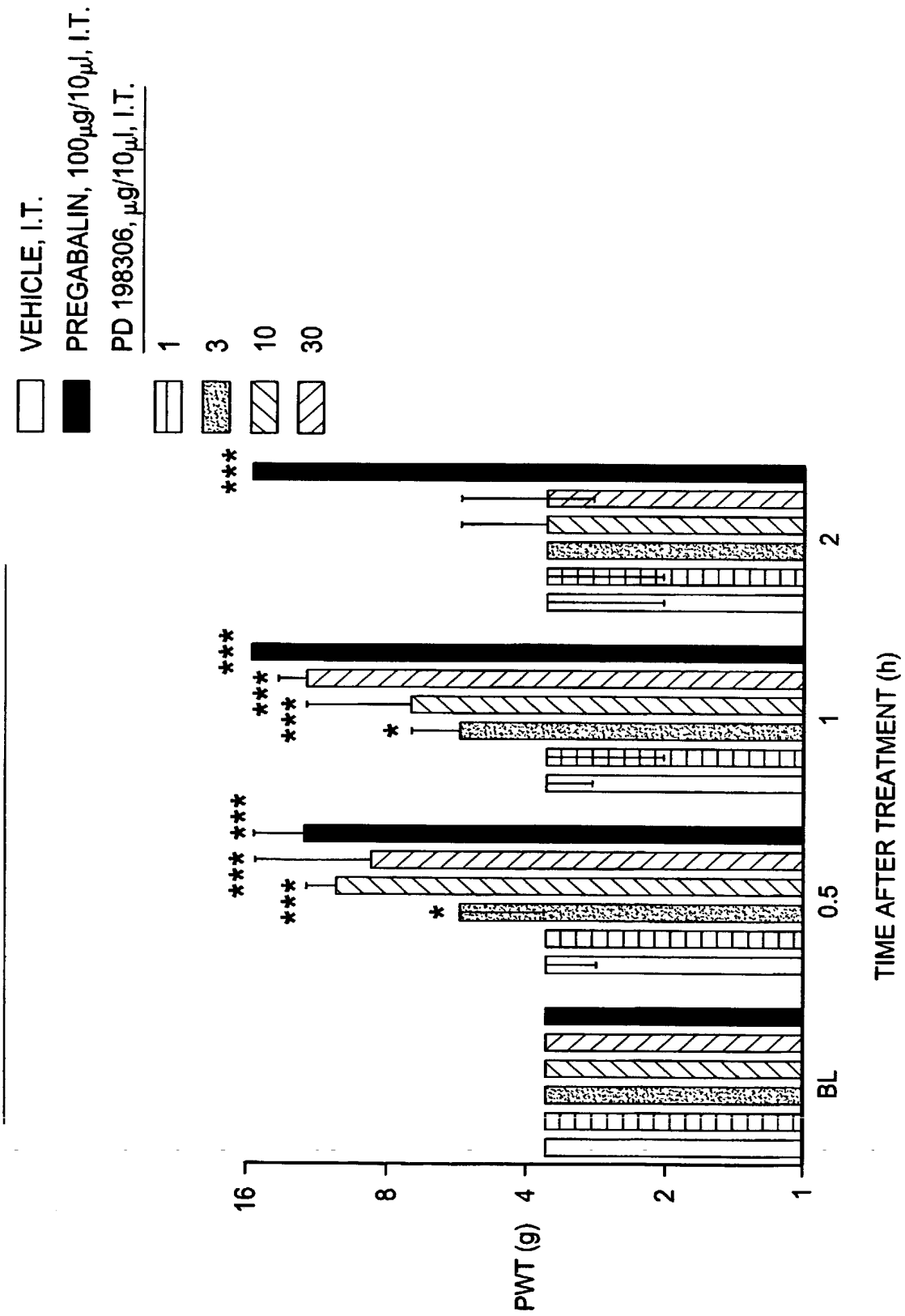


FIG. 5 EFFECT OF INTRATHECAL (i.t.) ADMINISTRATION OF PD 198306 ON CCI-INDUCED STATIC ALLODYNIA

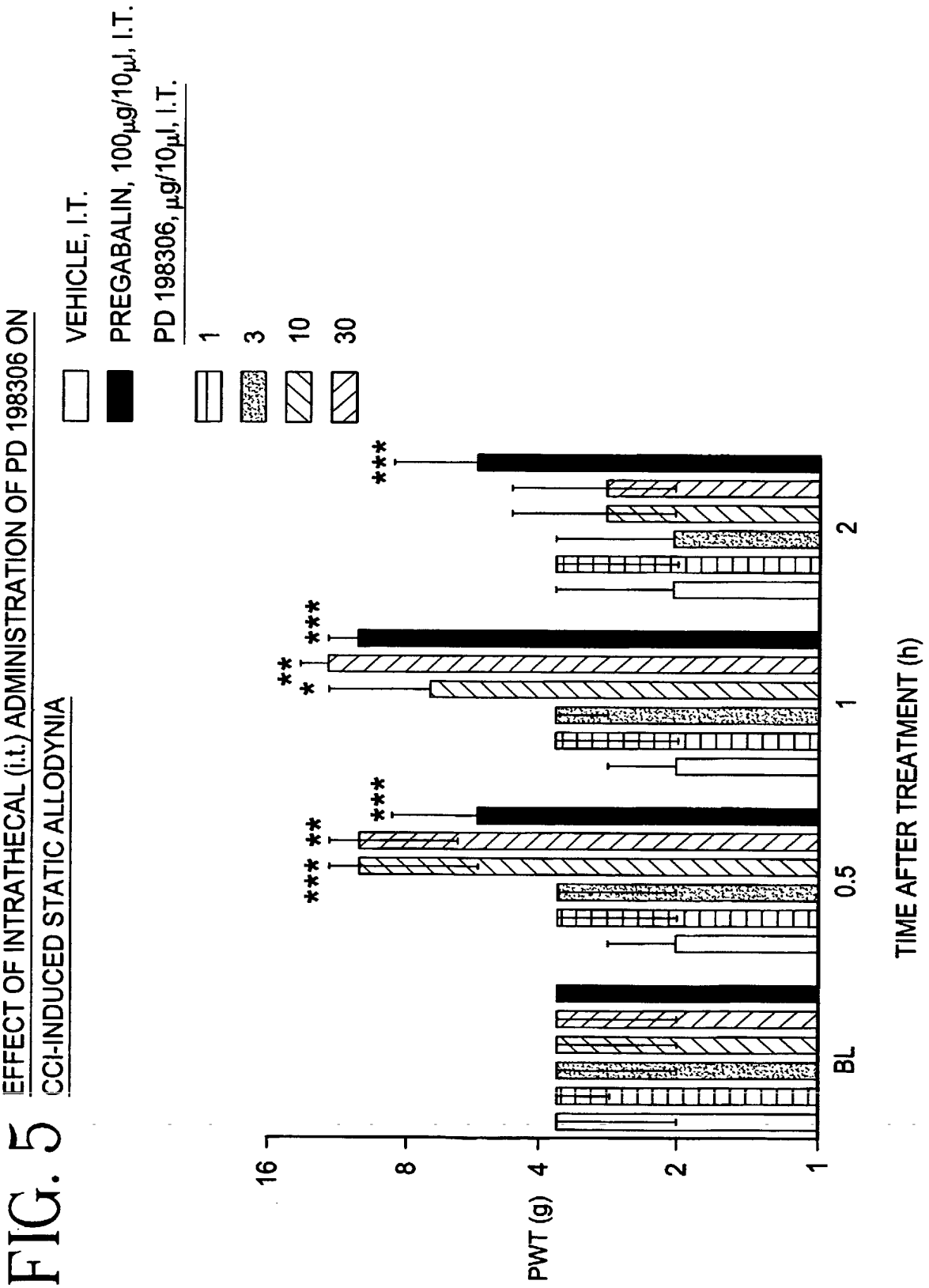


FIG. 6 EFFECT OF INTRAPLANTAR (i.p.l.) ADMINISTRATION OF PD 198306 ON STREPTOZOCIN-INDUCED STATIC ALLODYNIA

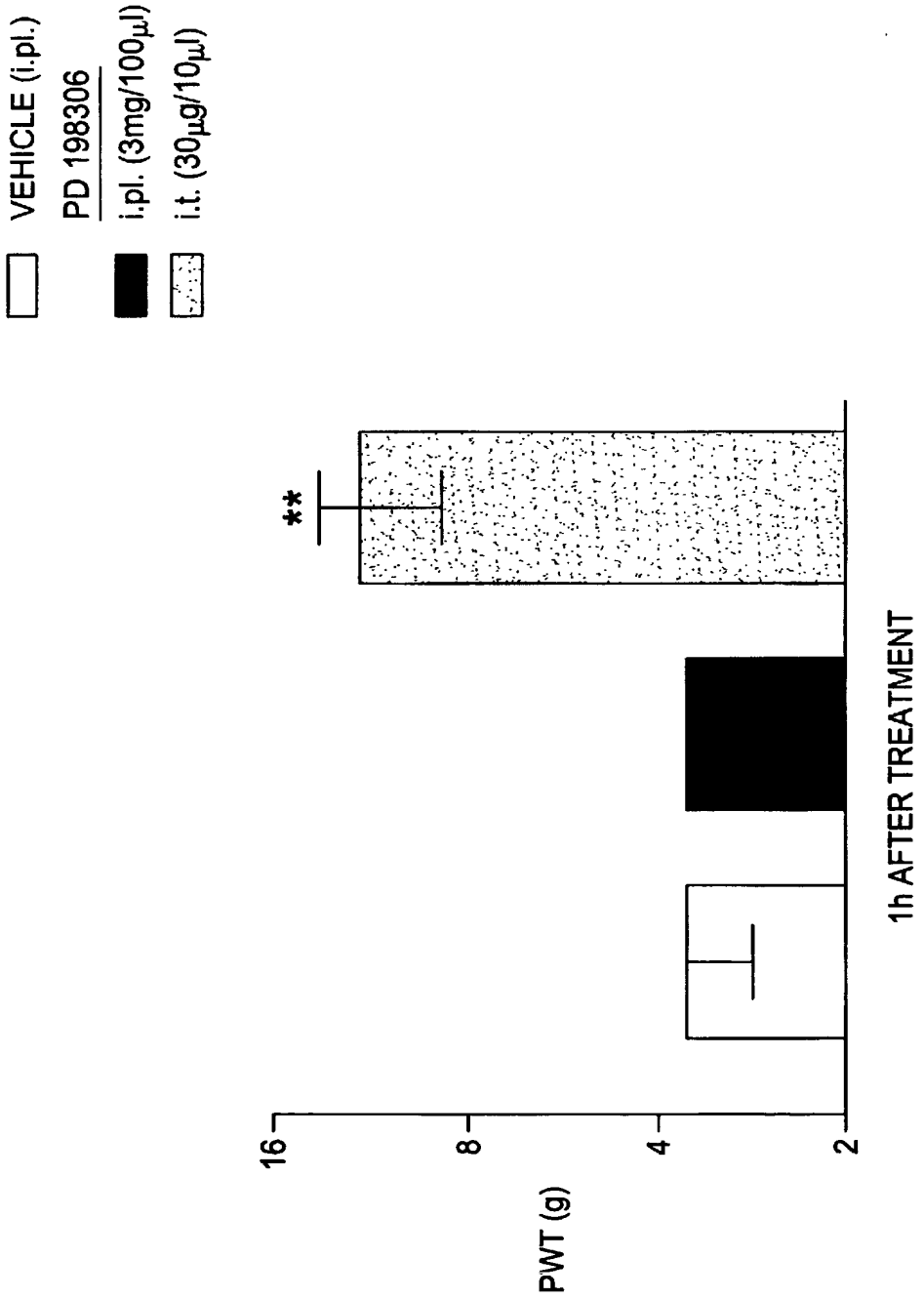


FIG. 7 EFFECT OF INTRAPLANTAR (i.p.) ADMINISTRATION OF PD 198306 ON CCI-INDUCED STATIC ALLODYNIA

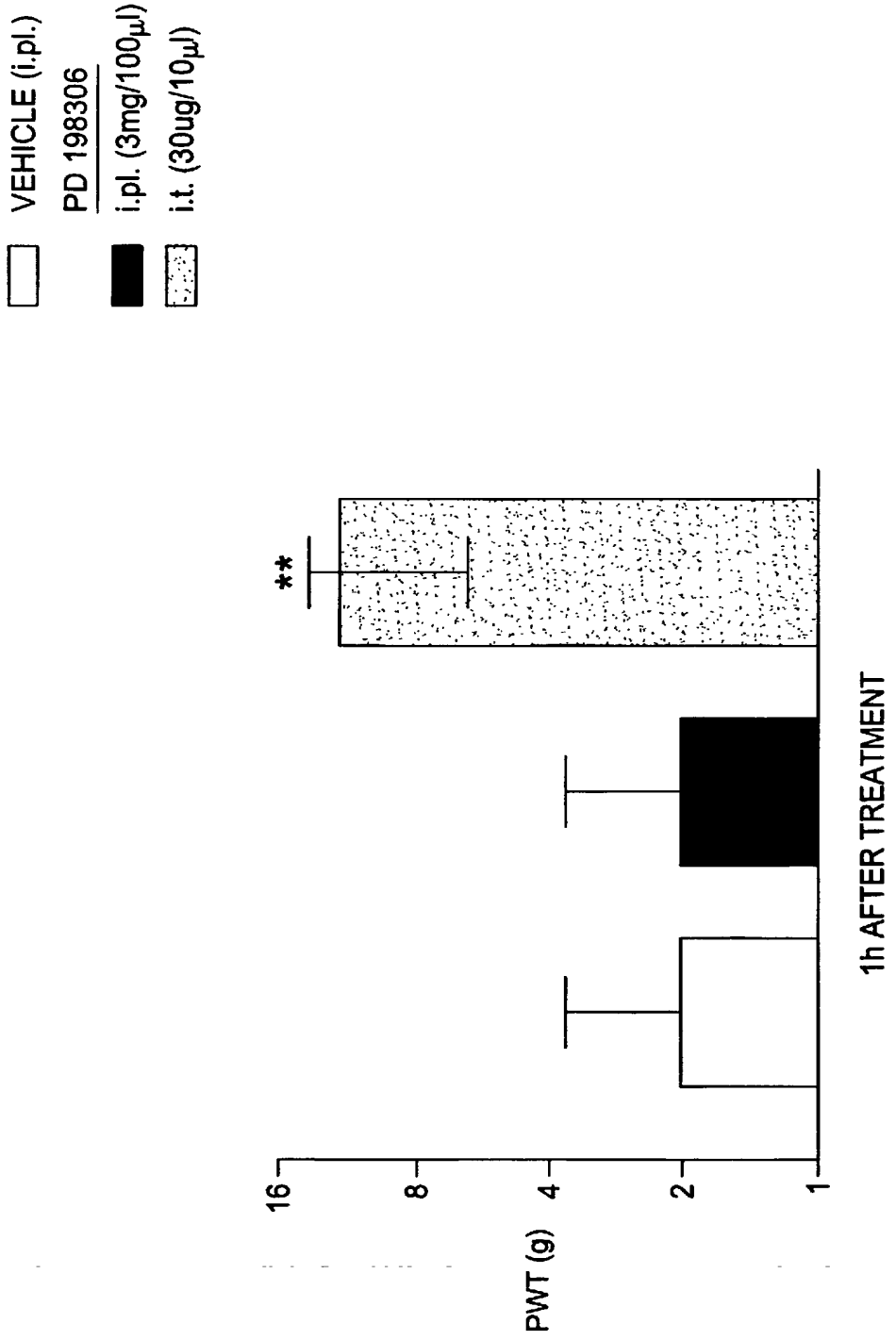
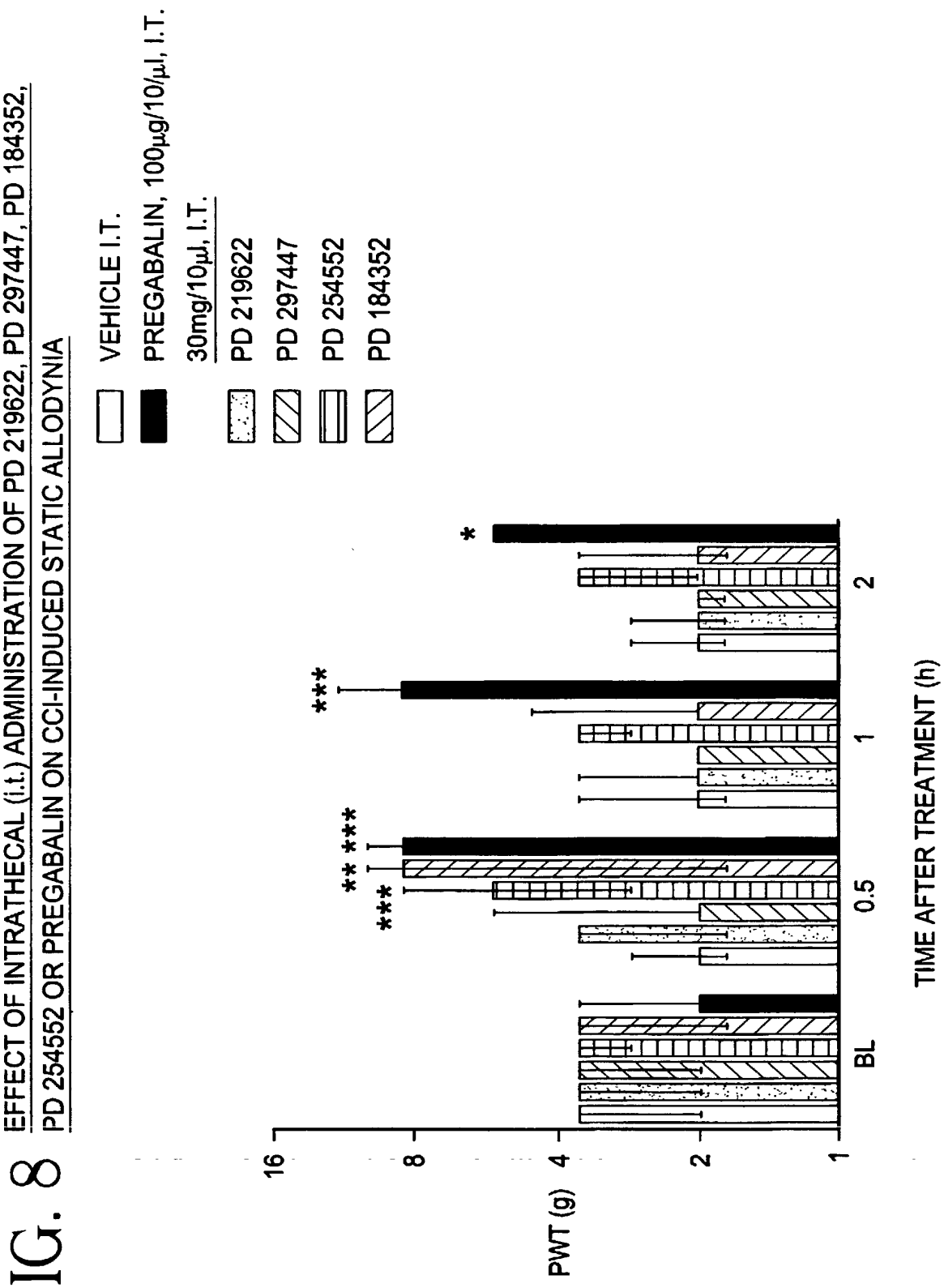


FIG. 8 EFFECT OF INTRATHECAL (i.t.) ADMINISTRATION OF PD 219622, PD 297447, PD 184352, PD 254552 OR PREGABALIN ON CCI-INDUCED STATIC ALLODYNIA



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Docket No.
A0000104-01-SMH

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:
METHOD FOR TREATING CHRONIC PAIN USING MEK INHIBITORS

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on 05 July 2000 As United States Application No. _____ or PCT International Application Number PCT/US00/18346
and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Applications			Priority Not Claimed
(Number)	(Country)	(Day/Month/Year Filed)	☐
(Number)	(Country)	(Day/Month/Year Filed)	☐
(Number)	(Country)	(Day/Month/Year Filed)	☐

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

60/144,403	16 July 1999
(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

PCT/US00/18346	05 July 2000	Pending
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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